On the synthesis and characterisation of some novel potential narcotic analgesics

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Award date:
1989

Awarding institution:
University of Bath

On The Synthesis And Characterisation

Of Some Novel Potential Narcotic Analgesics.

Thesis

Submitted by P. Cittern B.Sc. for the Doctor of Philosophy

of the University of Bath 1989.

This research has been carried out under the supervision of

Dr.A.F. Casy, Dr.G.H. Dewar and Dr.R.T. Parfitt.

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ACKNOWLEDGEMENTS

The author would like to express his thanks to Dr. Alan F. Casy, Dr. George H. Dewar and Dr. Robert T. Parfitt for their encouragement and helpful advice throughout the course of this research.

Thanks are also due to the other members of staff in the Department of Pharmaceutical Chemistry for their support, and especially to Dr. R. Taylor for his enthusiasm and guidance during the early stages of the research.

Acknowledgement should also be given to Dr. V.K. Kapoor of the Department of Pharmaceutical Sciences at the University of Panjab, Chandigarh for his valuable assistance with the synthetic work associated with chapter three during the tenure of a sabbatical year at Bath.

Grateful thanks also to Dr. A.E. Jacobson of the Institutes of Health, Bethesda for all of the analgesic evaluations.

To Mr. R. Hartell and Mr. D. Wood go my thanks for their skill in securing ^{13}C and ^{1}H NMR spectra.

The author would like to express his gratitude to Annette, Nicki and Michelle for typing the manuscript.

And finally, to my wife Gill for her support and patience throughout the past four years.

SUMMARY

This thesis concerns the synthesis and chemical characterisation of some novel synthetic and semi-synthetic narcotic analgesics. The thesis is divided into four chapters.

Chapter one concerns the synthesis of the 8-arylmorphan derivative 8-acetoxy-2-methyl-8-phenyl-2-azabicyclo[3.3.1]nonane, in eleven steps from hydroxyphenylacetic acid. This agent was examined for analgesic activity in rodents but was essentially inactive.

In chapter two the synthesis of some pethidine reverse ester and fentanyl analogues of 3-substituted quinuclidines is described. The fentanyl analogue 2-benzyl-3-(N-propionylanilino)quinuclidine was found to be approximately one tenth as active as morphine in rodent tests, but all other derivatives proved inactive.

Chapter three concerns the preparation of an optically pure series of (-)-5α,1'-methyleneoxy-6,7-benzomorphans, obtained from natural dihydrocodeinone. This series of compounds was exemplified by the (-)-8-hydroxy-5α,1'-methyleneoxy-2-methyl-9α-propyl-6,7-benzomorphan which had a level of analgesic activity two thirds that of morphine in rodent tests. However, the other members of this series of compounds only exhibited low levels of activity.

The synthesis, resolution and chemical characterisation of the (+) and (-) antipodes of the 1-trans-2,6-trimethyl analogue of the reverse ester of pethidine is undertaken in chapter four. This study was part of a larger analysis (undertaken elsewhere) on the effect of alkyl substitution in the piperidine ring of 4-phenylpiperidine analgesics. The more active antipode was the dextrorotatory one, which was shown to have the configuration 2S,6S, and these observations are consistent with the broad body of data secured from structure-activity analysis of compounds in this class.

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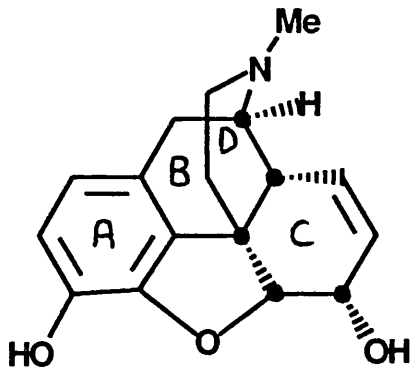
The research described in this thesis was carried out whilst the author was employed as an Experimental Officer in the Department of Pharmaceutical Chemistry at the University of Bath, during the period December 1980 to August 1985.

Chapters one, two and three cover research supervised largely by Dr.R.T. Parfitt and also by Dr.G.H. Dewar, during the period December 1980 to September 1984. Sections of chapter three were published in the Journal of Medicinal Chemistry, 29, 1929, (1986), and in the Indian Journal of Chemistry, 27B, 1039, (1988).

Chapter four covers research supervised by Dr.A.F. Casy during the period September 1984 to August 1985, and was published in the Journal of Pharmacy and Pharmacology, 38, 611, (1986).

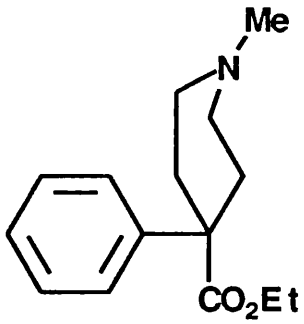
GENERAL INTRODUCTION

The structure of morphine 0.1 was elucidated in the 1920s by Robinson [1] and Schopf.[2]



0.1

Since then, a large number of synthetic and semi-synthetic narcotic analgesics have been produced and several have gained clinical acceptance. Pethidine 0.2 and pentazocine 0.3 are examples.



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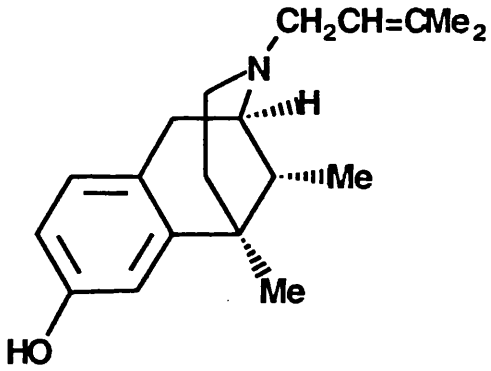
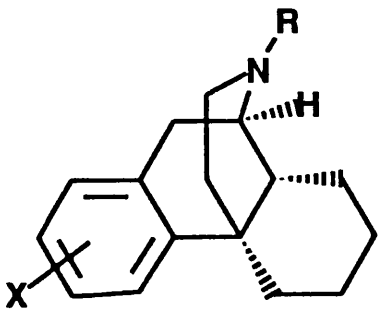


0.3

However, despite these advances, morphine and its derivatives (codeine, heroin) remain amongst the most clinically important drugs for the treatment and relief of chronic pain.

Many classes of synthetic analgesics, including 0.2 and 0.3, contain fragments of the structure of morphine [3] and it is therefore important to consider its structural aspects more fully.

Although morphine has 5 chiral centres (denoted ●), the steric constraints of the B/C ring junction (cis only) restrict the number of possible stereoisomers to 16. Morphine obtained from natural sources (the poppy Papaver somniferum) is exclusively the single laevorotatory enantiomer represented by 0.1. It is in this isomer that the analgesic activity resides. As is the case with other classes of synthetic analgesics, one optical isomer is generally responsible for the analgesic properties of the racemate. When the derivative retains the bulk of the morphinoid skeleton as in the morphinan (0.4) or 6,7-benzomorphan (0.5) series, it is the isomer which corresponds to the absolute configuration of naturally occurring morphine which is the analgesically active species.



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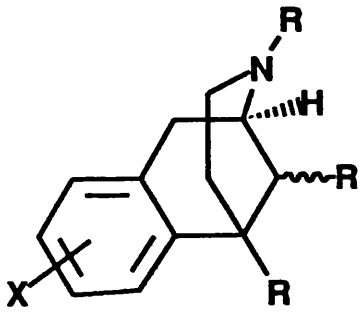


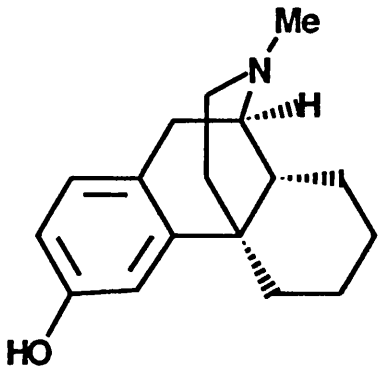
0.5

The dextrorotatory enantiomer of morphine has no analgesic properties and this is generally true of the other dextrorotatory morphinoid species. However, these compounds may possess other pharmacological activity, for example, anti-tussive properties.[4]

Once the structure of morphine had been elucidated, work began to produce modified derivatives in which the aim was to retain the analgesic properties of morphine and dissociate these from its undesirable side effects.

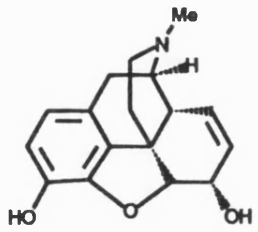
Before further discussion of these derivatives, the pharmacological effects of morphine should be noted. Morphine produces its analgesic effect by increasing the threshold at which pain is perceived. This is accompanied by a sedative, euphoric effect. Its major undesirable actions are respiratory depression and tolerance, which leads to the most widely known side effect of morphine : addiction.

Work on the production of new componds which might be free of, or have a reduced level of, side effects, was advanced by the discovery of the morphinan levorphanol (0.6).[4] This was found to be several times more potent than morphine, but with no greater level of side effects.

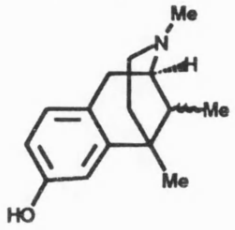


0.6

Other classes of synthetic analgesics have since produced compounds which have shown some dissociation of desirable and undesirable properties. These classes include the 6,7-benzomorphans, the arylmorphans, the phenylpiperidines, the 3,3-diphenylpropylamines and others. To illustrate their structural relationships to morphine, an example of each class is shown in figure 0.1.

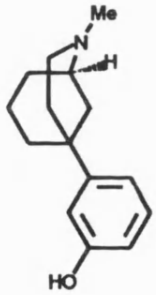


0.1 MORPHINE



6,7-BENZOMORPHANS

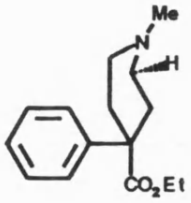
0.7 METAZOCINE



5-ARYLMORPHANS

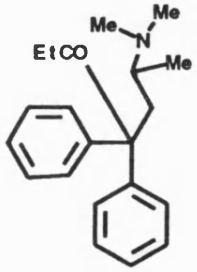
5(m-HYDROXYPHENYL)MORPHAN

0.8



4-PHENYLPIPERIDINES

0.2 PETHIDINE



3,3-DIPHENYLPROPYLAMINES

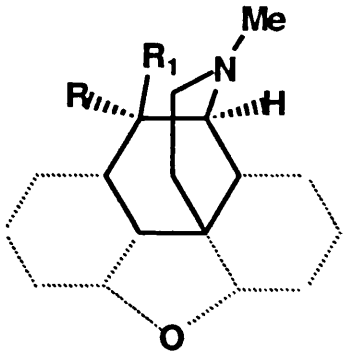
0.9 METHADONE

FIGURE 0.1

This thesis consists of four chapters, each of which relates to synthetic work carried out in a different area of the broad field of central analgesics research.

Chapter One concerns the synthesis of the 2-azabicyclo[3,3,1] non-8-one 0.10 and its subsequent conversion to the 8-phenyl-8-acetoxy derivative 0.12 via the alcohol 0.11.[5]

This particular azabicyclic skeleton (morphan) constitutes the central fragment of the morphine skeleton which has been drawn (dotted) surrounding 0.10, 0.11 and 0.12 below.



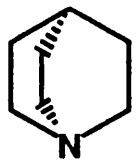
0.10 $R+R_1=O$

0.11 $R=Ph$ $R_1=OH$

0.12 $R=Ph$ $R_1=OCOMe$

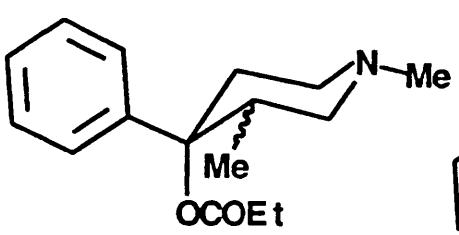
Although certain 5-arylmorphans possess significant analgesic activity [6], (0.8 being equipotent with morphine) no 8-arylmorphans have been examined for activity. The synthesis of 0.12 in Chapter One of this thesis is an attempt to examine the possibility of producing 8-arylmorphans as potentially active analgesics and was originally part of a larger scheme to examine the effect of repositioning the aromatic substituent to alternative sites on the morphan skeleton.[7]

Chapter Two concerns the synthesis of some potential narcotic analgesics based on quinuclidine 0.13.



0.13

Quinuclidines may be considered as analogues of piperidines in which both rings are constrained in boat conformations. Narcotic analgesics based on 4-substituted piperidines are numerous, pethidine 0.2, prodine 0.14 and fentanyl 0.15 being examples.



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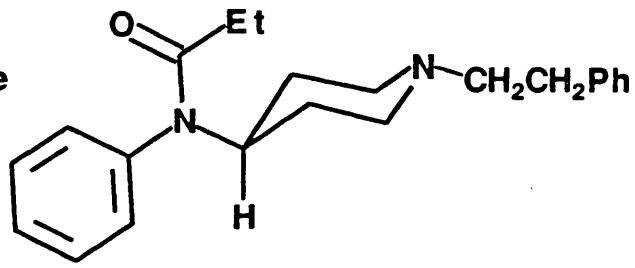
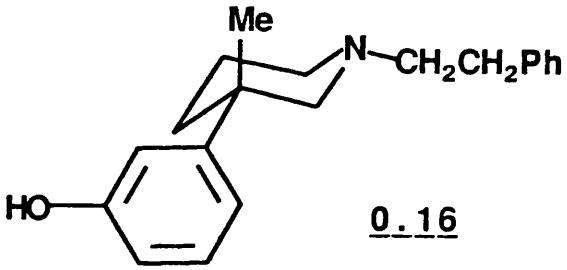


0.15

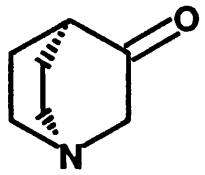
Certain 3-substituted piperidines also exhibit weak activity, for example 0.16.[8]



0.16

Quinuclidines analogous to a constrained conformation of 3-aryl piperidines are synthetically accessible via 3-quinuclidone 0.17.

Any analgesic activity exhibited by these analogues e.g. 0.18 may shed light on the opioid receptors conformational preferences for piperidine based analgesics.



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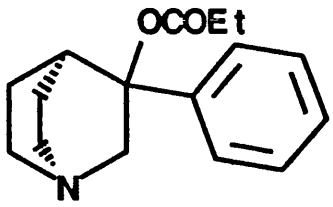
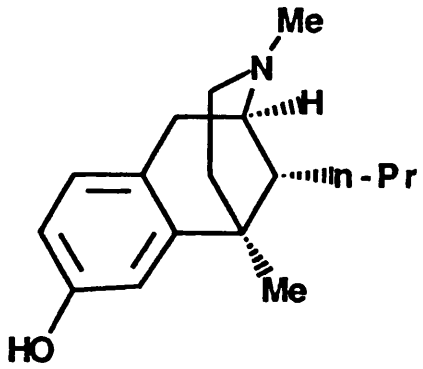


0.18

Chapter Three

The 6,7-benzomorphans are well documented as an important class of narcotic analgesics, and includes derivatives with pure agonist and mixed agonist/antagonist properties.[3] Since their invention in the 1950s, a large number of synthetic variations have been effected in an effort to separate their desired analgesia from physical dependence and other undesired properties.[10] Optical resolution producing pure optical isomers is another approach.[11] Certain optically pure (-)-6,7-benzomorphans have been shown to be without physical dependence capacity (PDC) in rhesus monkeys. In particular, the (-)-5-methyl-9α-propyl-6,7-benzomorphan 0.19 has been shown to warrant further investigation.[12] Chapter Three concerns the synthesis of a novel and optically pure laevo series of 'furanobenzomorphans' 0.20, which may be considered analogous to 0.19.[13]



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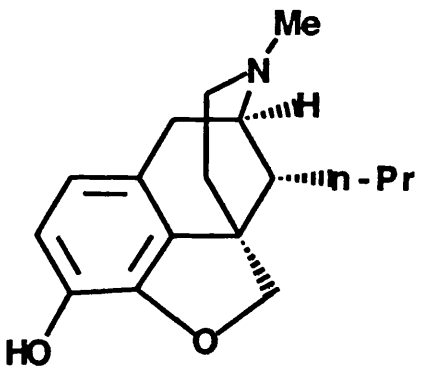
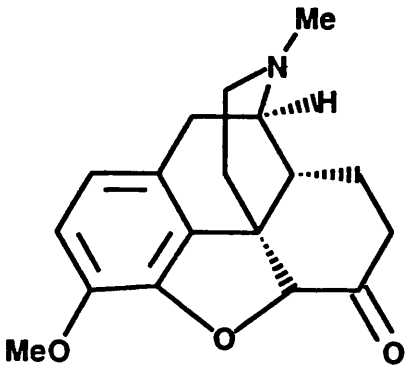


0.20

0.20 and its derivatives were produced by a four stage conversion of natural dihydrocodeinone 0.21, rather than by using a more conventional synthetic route followed by optical resolution of the resulting diastereomeric salts (scheme 0.1).



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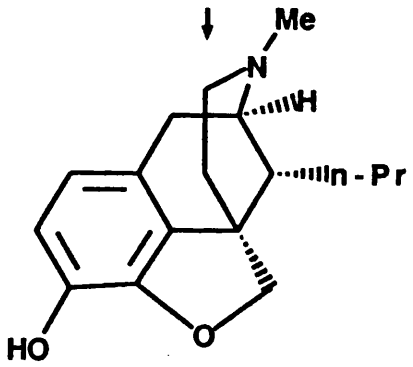
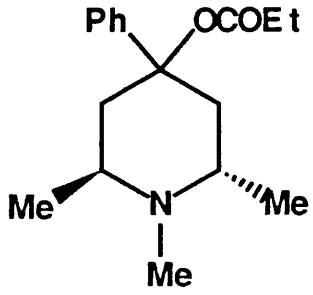


0.20

SCHEME 0.1

Chapter Four concerns the preparation, resolution and stereochemical characterisation of the (+) and (-) antipodes of the trans-2,6-dimethyl analogue (0.22) of the reversed ester of pethidine.



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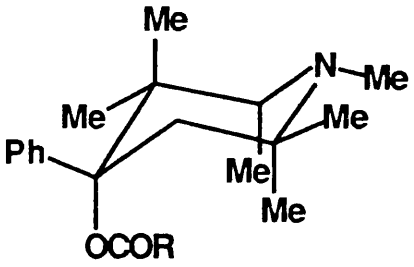
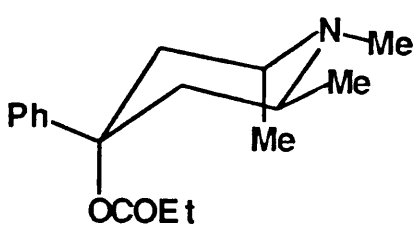


0.23

This study was part of a larger analysis (undertaken elsewhere) on the effect of alkyl substitution in the piperidine ring of 4-phenylpiperidine analgesics.[14,15] The overall analysis has defined the absolute orientation of methyl substituents that favour or have a minor influence on ligand-receptor interactions and thus influence analgesic activity. These allowed orientations are illustrated in 0.23. Following this model, the 2 antipodes of 0.22 (0.24 and 0.25) should show a large potency difference, with the more active form having the 2S,6S configuration (as depicted in 0.24).



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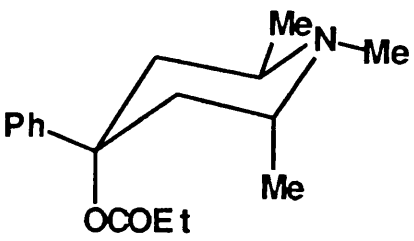

0.25

To confirm that the model is valid for 0.22, its initial synthesis, followed by resolution of the 2 antipodes, was undertaken. This was followed by X-ray crystallography of one antipode to confirm the absolute configuration of the more analgetically active species.[16]

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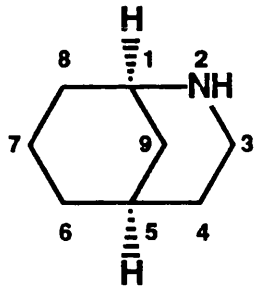
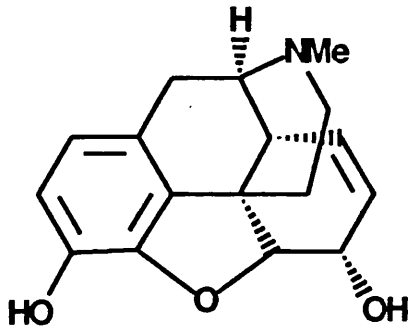
2-AZABICYCLONONANE INTRODUCTION

Morphan, [2-azabicyclo[3,3,1]nonane (1.1)], constitutes an important structural fragment of morphine 1.2, and as such is a potential substrate for elaboration into more complex, novel molecules with potential analgesic activity.



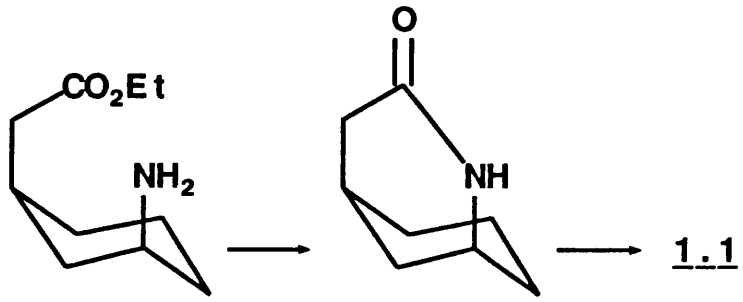
1.1



1.2

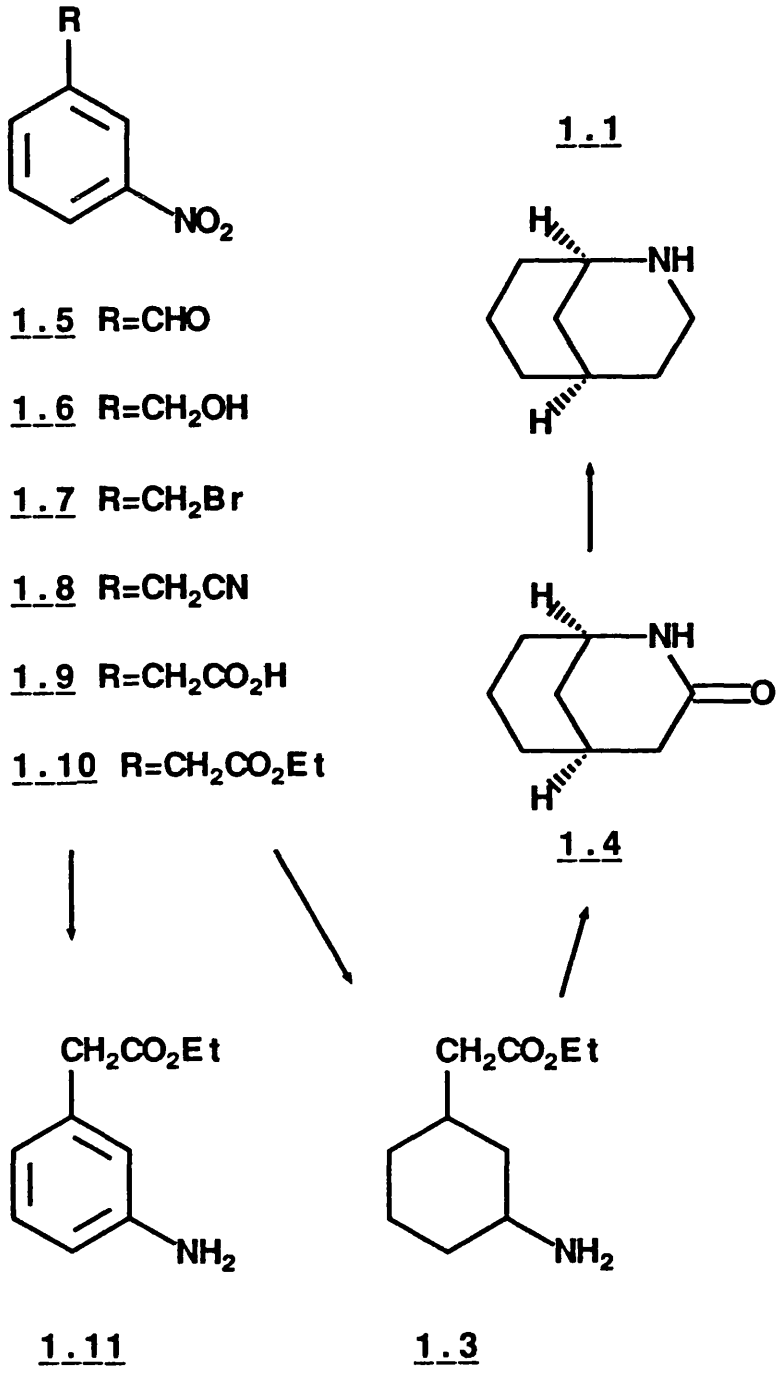
Various methods have been used for the synthesis of morphans over the past 40 years. Several of these have been chosen and illustrated with example syntheses.

In the late 1940s [1,2], the earliest successful attempts to synthesise the basic morphan skeleton utilised the lactamisation of ethyl cis-3-aminocyclohexane acetate 1.3, followed by reduction of the resulting lactam 1.4, either catalytically or with lithium aluminium hydride (LAH).



1.3 1.4

1.3 was prepared *via* 2 similar routes, both of which utilised m-nitrobenzaldehyde as precursor. The first (illustrated in scheme 1.1[1]) started with the reduction of m-nitrobenzaldehyde 1.5 to the corresponding alcohol 1.6 with aluminium isopropoxide. Conversion of 1.6 to the alkyl bromide 1.7 took place quantitatively with HBr in benzene. Conversion of 1.7 to the cyano derivative 1.8 followed by acid hydrolysis gave the acid 1.9. Esterification with ethanolic HCl gave ethyl m-nitrophenylacetate 1.10. Catalytic hydrogenation of 1.10 over Adams catalyst in glacial acetic acid gave the required ethyl cis-(3-aminocyclohexyl)acetate 1.3. Use of ethanol as solvent in place of acetic acid gave only the aromatic amine 1.11 presumably due to poisoning of the catalyst by 1.11. Larger scale reductions in glacial acetic acid yielded mixtures of ester 1.3 and lactam 1.4. Ester 1.3 was also partially lactamised to 1.4 by heating and subsequent distillation. LAH reduction of 1.4 in dioxan gave the required 2-azabicyclo[3.3.1]nonane 1.1 . The overall yield of 1.1, from m-nitrobenzaldehyde was approximately 6%.

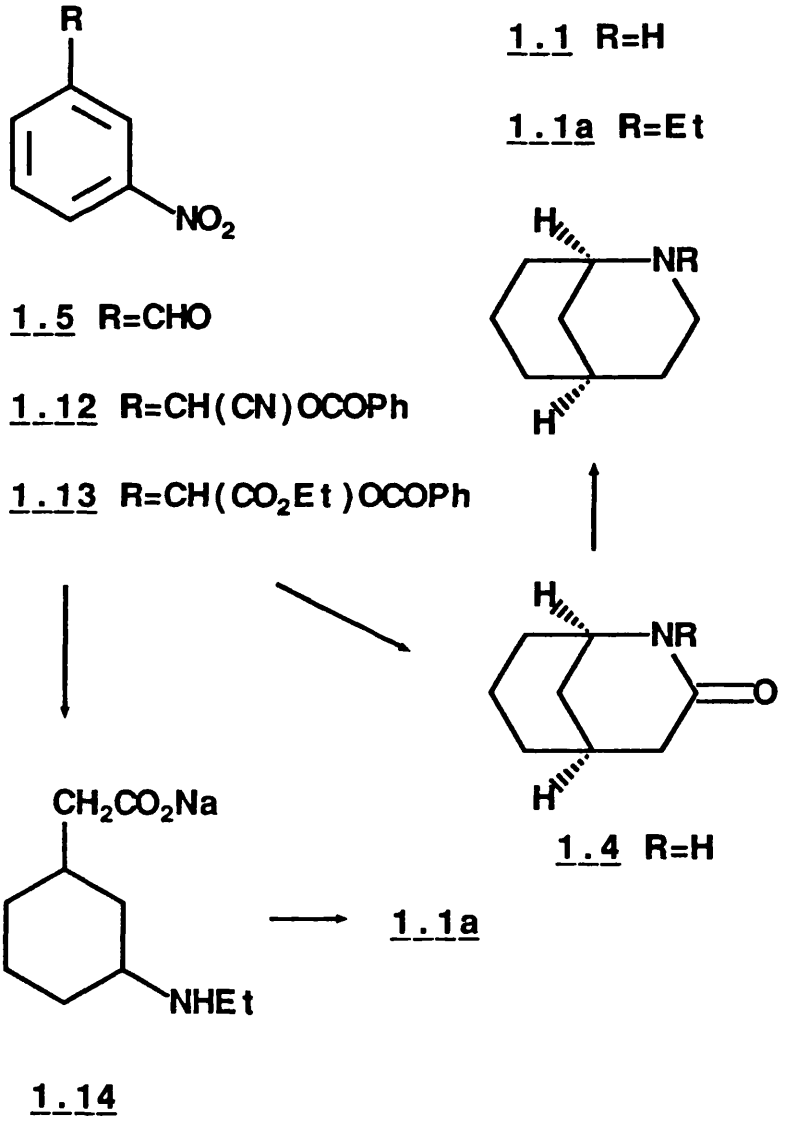

R
NO2
1.1
H
NH
H
1.5 R=CHO
1.6 R=CH2OH
1.7 R=CH2Br
1.8 R=CH2CN
1.9 R=CH2CO2H
1.10 R=CH2CO2Et
H
NH
O
H
1.4
CH2CO2Et
CH2CO2Et
NH2
NH2
1.11
1.3

SCHEME 1.1 [1]

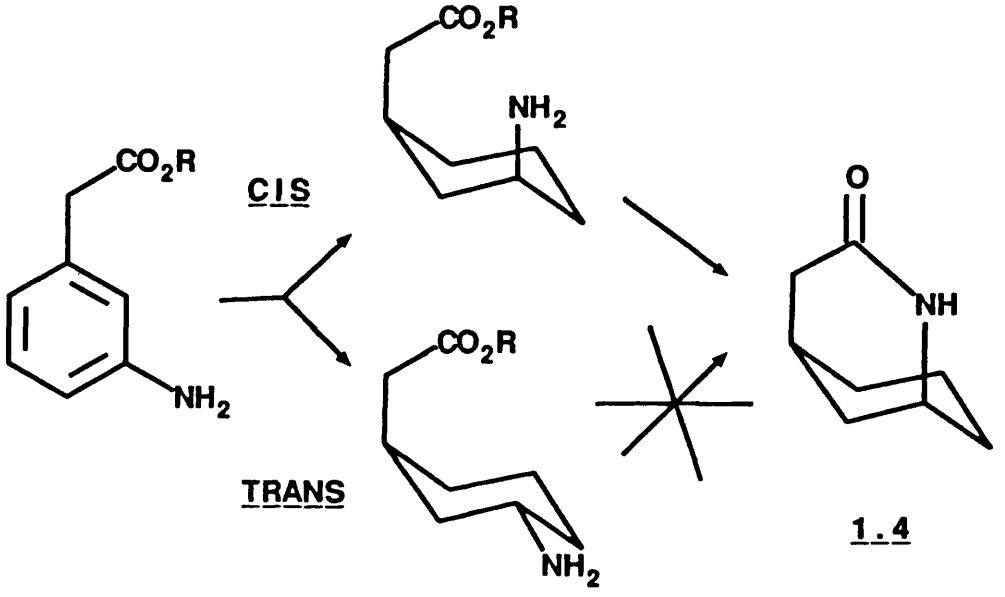
The second synthesis (shown in scheme 1.2[2]) again utilised m-nitrobenzaldehyde as starting material. Treatment with benzoyl chloride and sodium cyanide gave m-nitro-O-benzoylmandelonitrile 1.12. Alcoholysis of 1.12 in ethanolic HCl gave ester 1.13. Catalytic hydrogenation of 1.13 over Raney nickel in ethanol at 120°C in the presence of sodium carbonate gave largely the N-ethyl-cis-3-aminocyclohexaneacetic acid 1.14, which lactamised on heating to 215°C to give N-ethylmorphan 1.1a.

Catalytic hydrogenation of 1.13 over Raney nickel in tert-butanol gave the lactam 1.4 directly. 1.4 was hydrogenated over a copper chromite catalyst to give the required 2-azabicyclo[3.3.1]nonane 1.1. The overall yield of 1.1 from m-nitrobenzaldehyde in this sequence was approximately 10%.

These 2 schemes offer a similar approach to the synthesis of morphan 1.1. However, they suffer from 2 major disadvantages. Firstly, reduction of the aromatic nitro/amino ester gives a proportion of aminocyclohexyl ester in the trans configuration which cannot lactamise for steric reasons (scheme 1.1a).


R
NO2
1.1 R=H
1.1a R=Et
H
NR
H
1.5 R=CHO
1.12 R=CH(CN)OCOPh
1.13 R=CH(CO2Et)OCOPh
H
NR
O
H
1.4 R=H
CH2CO2Na
1.1a
NHEt
1.14

SCHEME 1.2 [2]



SCHEME 1.1a

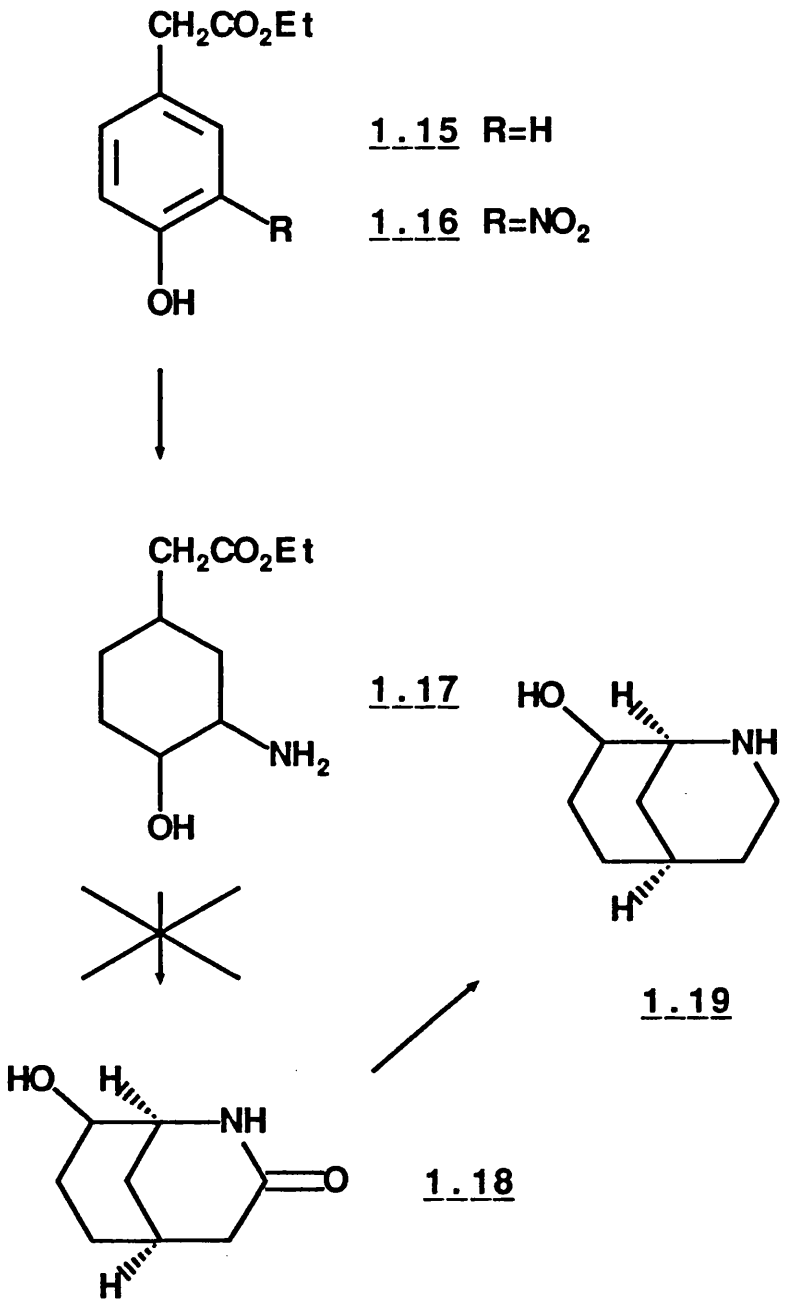
Approximately 25 % of the unwanted trans aminocyclohexyl ester was produced in schemes 1.1 and 1.2, further contributing to their overall low yields.

The second disadvantage of these syntheses is that the final product 1.1 is devoid of functional groups, restricting the production of more complex structures with potential analgesic activity.

Methods available for the synthesis of functionalised 2-azabicyclo [3.3.1]nonanes will now be discussed.

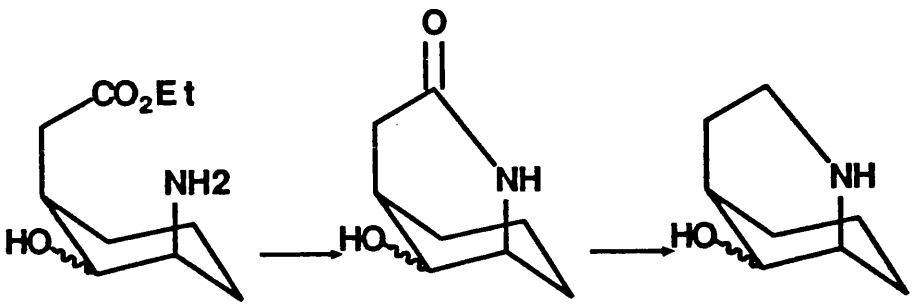
The first, illustrated in scheme 1.3 and attempted in this laboratory[2a] allows the incorporation of a hydroxyl group in the final product at position 8. Nitration of ethyl 4-hydroxyphenyl acetate 1.15 yielded predominantly the m-nitro derivative 1.16. The catalytic hydrogenation of 1.16 using a range of experimental conditions (catalyst, solvent, temperature and pressure) led to the reduction of the aromatic ring in most cases. However, cyclised products were not obtained either directly from the reduction, or after heating or distillation of the reduced products.

The required 8-functionalised morphan was eventually obtained by another route (see discussion) and consequently this lactamisation method was not pursued further. However, it has been reported here for completeness as a potential route to functionalised morphans. Oxidation of 1.19 to the keto derivative would allow more complex structures to be developed, for example, compounds produced via Grignard reactions (see discussion).


CH2CO2Et
R
OH
1.15 R=H
1.16 R=NO2
CH2CO2Et
NH2
OH
1.17
HO
H
NH
H
1.19
HO
H
NH
O
H
1.18

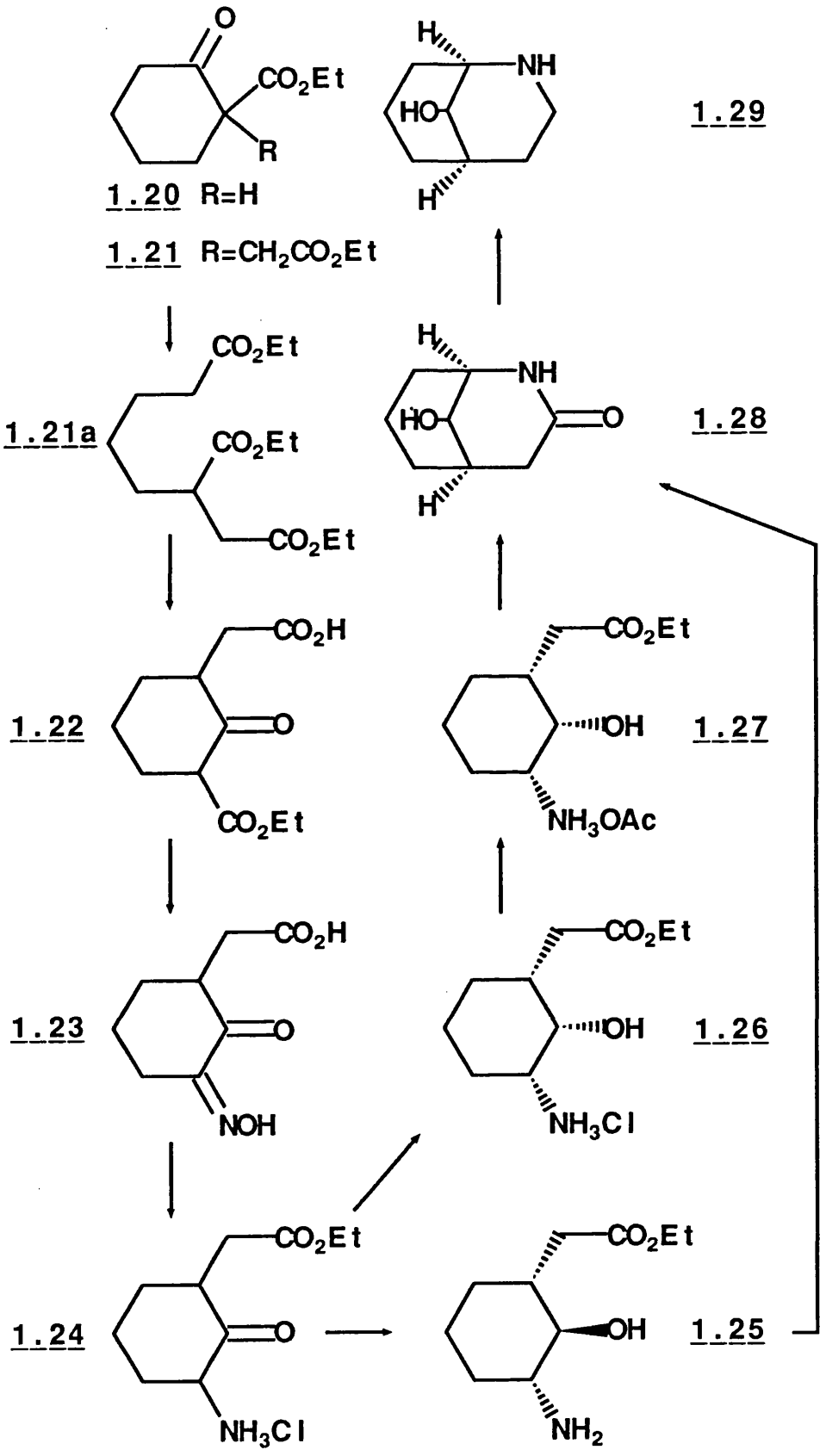
SCHEME 1.3 [2a]

In the mid 1950s[3], an approach to the synthesis of the 9-hydroxy morphan 1.29 utilised the lactamisation of cis-ethyl 3-amino-2-hydroxycyclohexane acetate 1.25.



1.25 1.28 1.29

However, unlike the earlier examples, the intermediate amino ester 1.25 was not obtained via reduction of a suitable aromatic precursor. Instead, 2-carbethoxycyclohexanone 1.20 was chosen as starting material (scheme 1.4). Alkylation of 1.20 with sodium ethoxide and ethyl bromoacetate gave diester 1.21. Alcoholysis of 1.21 with sodium ethoxide in ethanol followed by ring closure and hydrolysis of the intermediate open chain triester 1.21a gave the mono acid 1.22. Replacement of the carbethoxy group in 1.22 by oximation gave oxime 1.23. Catalytic hydrogenation of 1.23 over palladium on carbon followed by treatment with ethanolic HCl gave amino ester hydrochloride 1.24. Sodium borohydride reduction of 1.24 in ethanol gave the alcohol 1.25 which lactamised on heating to 200°C. The isomeric alcohol 1.26 was obtained by hydrogenation over platinum on carbon using H_2O as solvent. However 1.26 could not be lactamised in the normal manner.


O
CO2Et
R
1.20 R=H
1.21 R=CH2CO2Et
H
NH
HO
H
1.29
CO2Et
1.21a
CO2Et
CO2Et
1.28
CO2H
1.22
O
CO2Et
CO2Et
OH
1.27
NH3OAc
CO2H
1.23
O
NOH
CO2Et
OH
1.26
NH3Cl
CO2Et
1.24
O
NH3Cl
CO2Et
OH
1.25
NH2

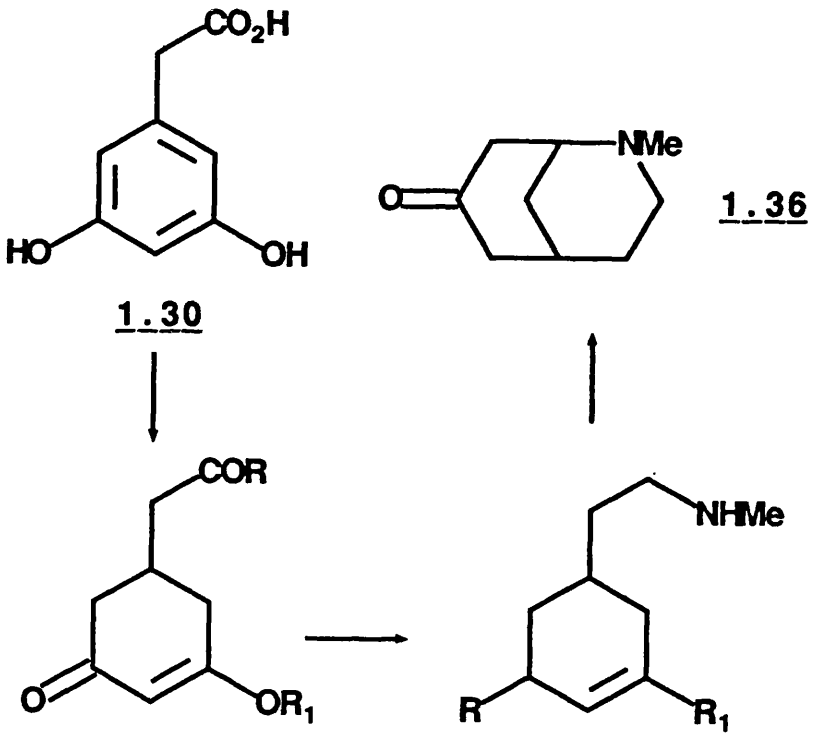
SCHEME 1.4 [3]

Instead, treatment of its hydrochloride with sodium acetate in ethanol afforded the acetate 1.27, which could be induced to lactamise by heating to give 1.28.

LAH reduction of the resulting lactam 1.28 gave the 9-hydroxy-2-azabicyclo[3,3,1]nonane 1.29 in 23% yield. The overall yield of 1.29 from 2-carbethoxycyclohexanone was approximately 0.5%.

In the early 1970s[4], an alternative method of producing a 7-functionalised 2-azabicyclo[3,3,1]nonane skeleton was reported, utilising an intramolecular Michael-type cyclisation of 2-oxo-4-(N-alkylaminoethyl)cyclohexene 1.35 (scheme 1.5).

Starting from 3,5-dihydroxyphenylacetic acid 1.30, catalytic hydrogenation over rhodium on alumina in aqueous sodium hydroxide afforded 1,3-cyclohexanedione-5-acetic acid 1.31 (mono-enol form). Amide formation on 1.31 required the protection of the enolic-OH (by esterification) to prevent reaction with the amine. Once protected, reaction with methylamine followed by hydrolysis of the protecting group gave amide 1.32. Enol ether 1.33 was obtained by refluxing 1.32 in methanol containing p-toluenesulphonic acid (p-TSA). LAH reduction of the amide function in 1.33 gave amine 1.34. Hydrolysis in aqueous acid, followed by treatment with sodium hydroxide, then effected cyclisation via 1.35, to give 2-methyl-2-azabicyclo[3,3,1]nonan-7-one 1.36. The overall yield from 3,5-dihydroxyphenylacetic acid was 31%. The N-substituent could be varied by use of other amines at the amide formation stage.



1.31 R=OH R_1=H

1.32 R=NHMe R_1=H

1.33 R=NHMe R_1=Me

1.34 R=OH R_1=OMe

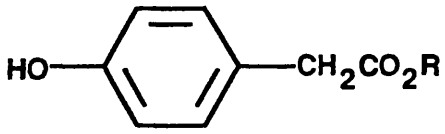
1.35 R=O R_1=H

SCHEME 1.5 [4]

In the mid 1970s[5], an alternative method of synthesis, yielding an 8-functionalised morphan, utilised the solvolysis of enol ether (and ethylene ketal) N-chloramines in trifluoroacetic acid and methanol. The N-chloramines were prepared in 7 steps from hydroxyphenylacetic acid 1.37. (Scheme 1.6 illustrates one of the 2 major reaction pathways used.)

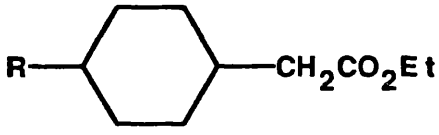
Esterification of 1.37 with ethanol and H_2SO_4 gave ethyl ester 1.38. Catalytic hydrogenation of the aromatic ring in 1.38 over Raney nickel in ethanol at high pressure and temperature gave ethyl 4-hydroxycyclohexyl acetate 1.39. Oxidation of the hydroxyl group in 1.39 with acid dichromate gave ketone 1.40. Reaction of 1.40 with trimethylorthoformate and methanol in the presence of p-TSA protected the keto group as its enol ether 1.41. Reaction of the ester group with methylamine and sodium methoxide in methanol gave amide 1.42 which was reduced to the amine 1.43 with LAH in THF. Quantitative conversion to the N-chloramine 1.44 was achieved by treatment of 1.43 with sodium hypochlorite solution. Solvolysis of 1.44 in trifluoroacetic acid gave cyclic enol ether 1.45, which after hydrolysis afforded N-methyl-2-azabicyclo[3.3.1]non-8-one 1.46.

Use of the ethylene ketal protecting group in place of the enol ether similarly afforded 1.46. The overall yield in each case was approximately 20% from hydroxyphenylacetic acid (1.37).



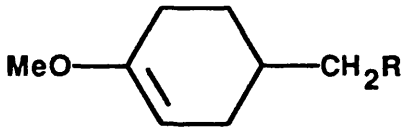
1.37 R=H

1.38 R=Et



1.39 R=OH

1.40 R=O



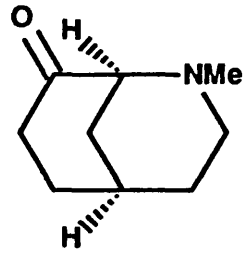
1.41 R=CO_2Et

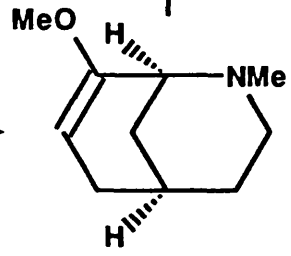
1.42 R=CONHMe

1.43 R=CH_2NHMe

1.44 R=CH_2NCIMe

1.46





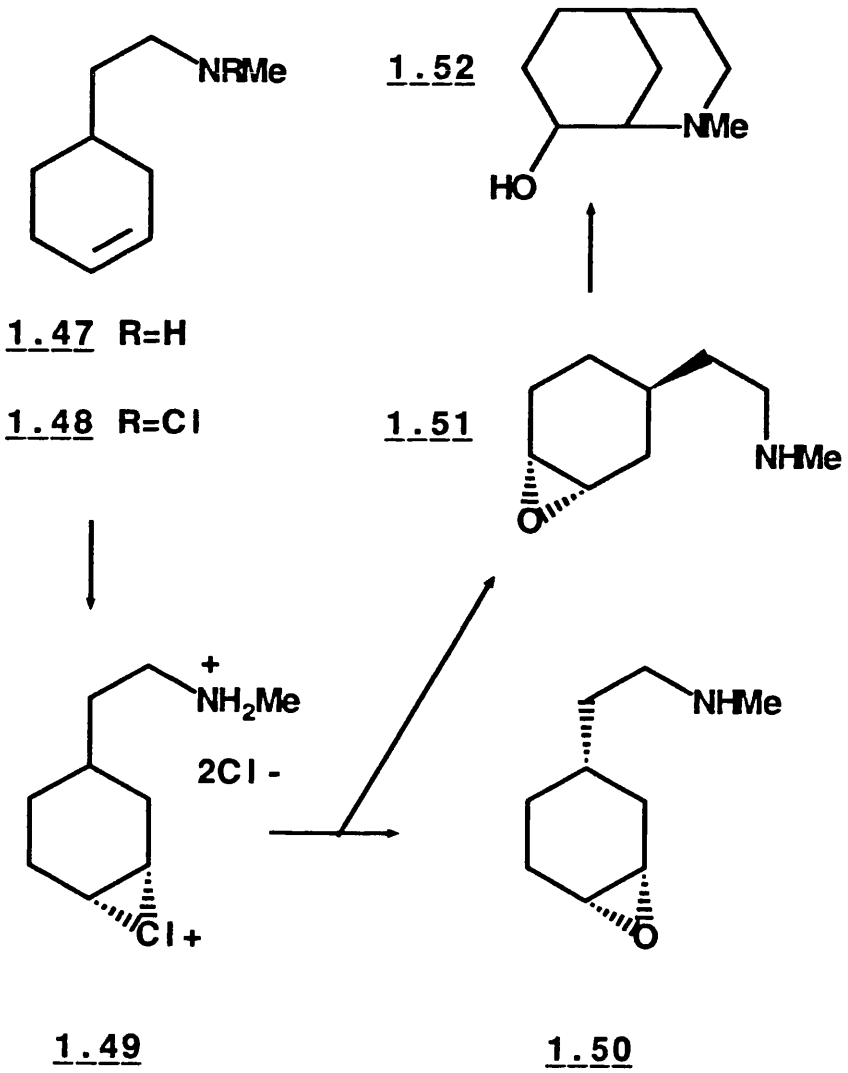
1.45

SCHEME 1.6 [5]

Another solvolytic method of synthesis of a 6-functionalised morphan utilised the solvolysis of 4-(N-chloromethylaminoethyl) cyclohexane 1.48 in dilute acid (scheme 1.7[6]).

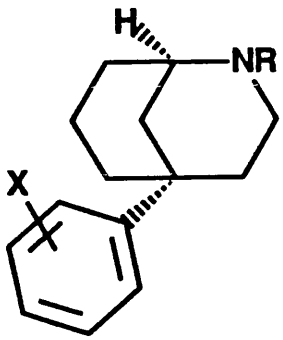
Thus, N-chlorination of 1.47 gave the chloramine 1.48. On treatment with aqueous acid this rearranged to 1.49. Treatment of 1.49 with base gave the isomeric epoxides 1.50 and 1.51. 1.51 was not isolated but cyclised to the required 6-hydroxy-2-azabicyclo[3.3.1]nonane 1.52. In practice, treatment of 1.48 with 1M H_2SO_4 gave a 1:2:4 mixture of starting amine 1.47, morphan 1.52 and epoxide 1.50. 1.52 was obtained in 37% yield after purification.

Starting amine 1.47 might also be produced using an abbreviated version of scheme 1.6 by hydrolysis and reduction of 1.43.

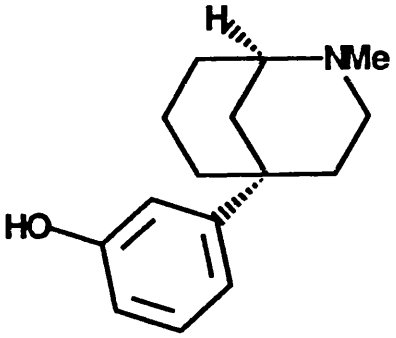

NRMe
1.52
NMe
HO
1.47 R=H
1.48 R=Cl
1.51
NHMe
O
+
NH2Me
2Cl -
NHMe
Cl +
O
1.49
1.50

SCHEME 1.7 [6]

A notable example of a series of synthetic analgesics based on the 2-azabicyclo[3.3.1]nonane system are the 5-arylmorphans 1.53.

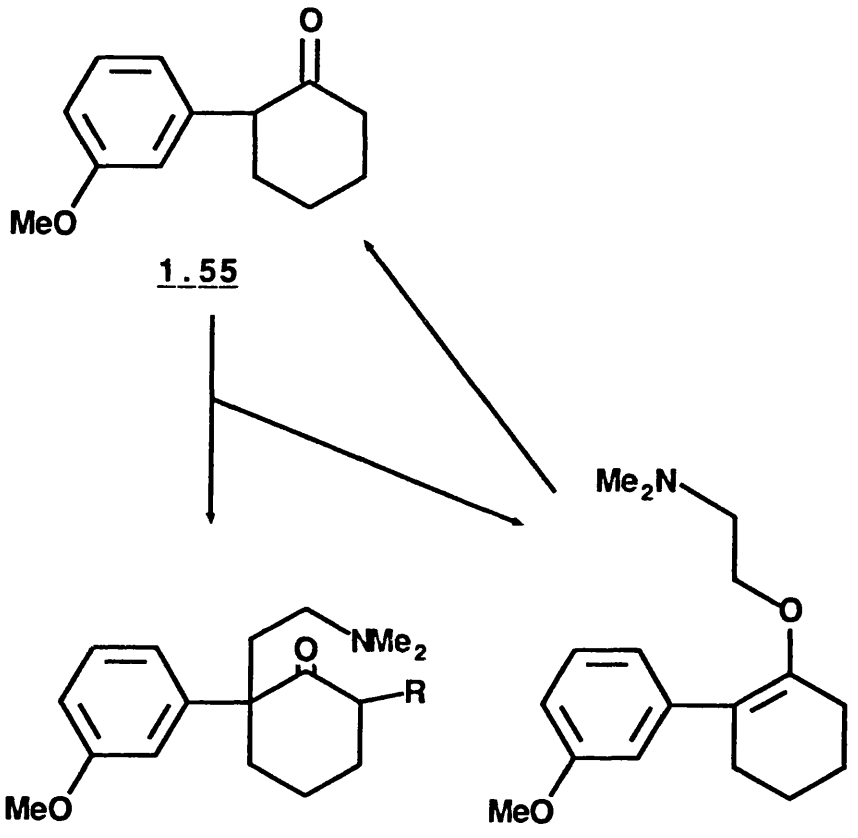


1.53



1.54

Several of these, notably 1.54, have been investigated [7-10] and found to be highly potent in rodent tests. The synthesis of 5-(m-hydroxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane 1.54 is illustrated in scheme 1.8.[7] Alkylation of 2-(m-methoxyphenyl) cyclohexanone 1.55 with 2-chloro-N,N-dimethylethylamine gave 20% of wanted C-alkylated product 1.56 and 60% of O-alkylated product 1.57 from which 1.55 could be regenerated by acid hydrolysis. Bromination of 1.56 in acetic acid followed by ring closure of the resultant α-bromo ketone 1.58 in aqueous ammonia, gave the wanted 5-(m-methoxyphenyl)-9-oxo-2-methyl)morphan methobromide 1.59. Dry distillation gave the base 1.60, which was converted to 1.61 by Wolff-Kishner reduction. Finally O-demethylation with HBr gave 1.54. The overall yield from 2-(m-methoxyphenyl)cyclohexanone was approximately 31%.

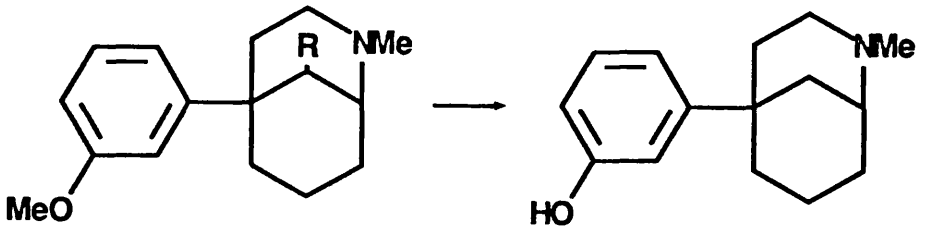


1.55

1.56 R=H

1.57

1.58 R=Br



1.59 R=O (methobromide)

1.54

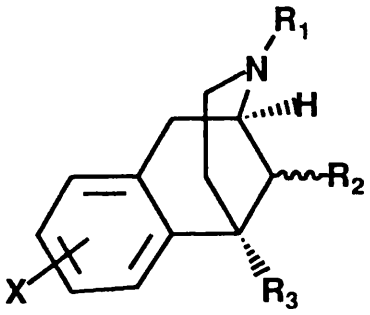
1.60 R=O (base)

1.61 $R=H_2$

SCHEME 1.8 [7]

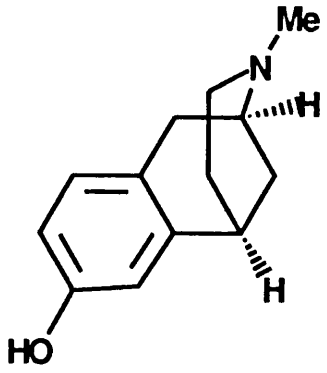
AZABICYCLONONANE DISCUSSION

It has been recognised for some time that not all of the chemical features of morphine 1.2, need be retained as a prerequisite for analgesic potency. For example, a large number of 6,7-benzomorphans 1.62, have been synthesised; many possess significant potency and several are in clinical use as narcotic analgesics.[11,12]



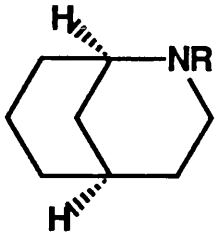
1.62

Further rationalisation of the 6,7-benzomorphan structure can still give rise to compounds which display analgesic action. For instance, 1.63 lacks many of the features of morphine yet is of greater potency.[13]



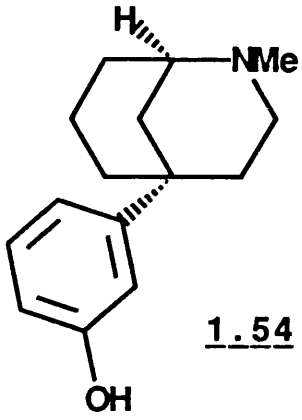
1.63

Modification of 1.63 by removal of the aromatic ring from its fused 6,7 position yields the morphan system 1.64. Examples of morphans which have the aromatic moiety in other positions (notably the 5 position) yet remain potent are known for example 1.54.[8]



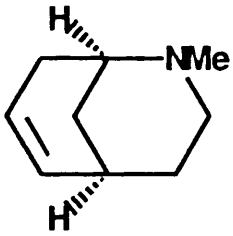
1.64 R=H

1.65 R=Me



1.54

However, morphans without aromatic substituents, for example, 1.64 and 1.65, or those with a 6,7 double bond as in 1.66, have been found to be inactive.[14]



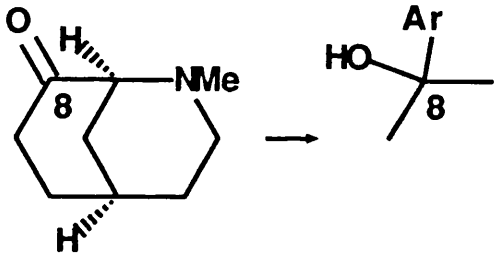
1.66

The presence of an aromatic ring in the morphan system has been demonstrated to be a necessity for analgesic activity; this is probably a binding requirement of the opioid receptors.[11]

Aims and Objectives

In order to investigate the effect on analgesic activity of moving the aromatic ring to alternate sites in the morphan system, the morphan-8-one 1.46 was required. 8-Aryl derivatives should then easily follow, for example via Grignard reactions.

1.46



The syntheses of 5, 6, 7, 8 and 9 functionalised morphans have been reported [3-7] and one method[5] was initially selected for use in this work (scheme 1.9). However, due to difficulties associated with the cyclisation stage using this method, an alternate route was developed in these laboratories (scheme 1.10). Both routes will be discussed.

The reported method of synthesis of 1.46 used an intramolecular cyclisation of the N-chloramine 1.72 under acidic solvolytic conditions. 1.46 was synthesised in 8 steps from commercially available 4-hydroxyphenylacetic acid.[5]

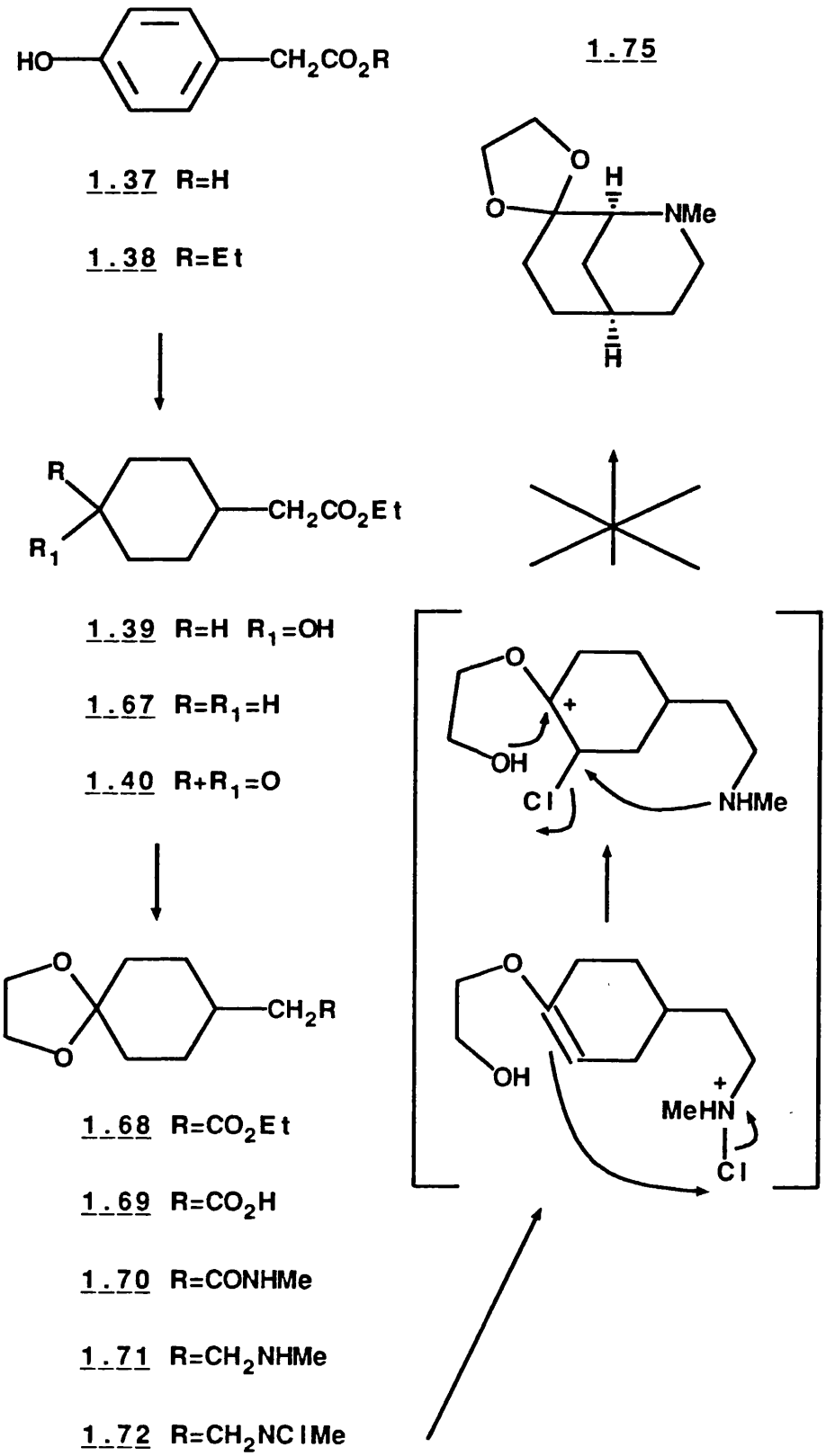
Attempted Synthesis of 1.46 via Solvolysis of 1.72. (Scheme 1.9[5])

Esterification of 4-hydroxyphenylacetic acid 1.37, as reported[5], in ethanol with H_2SO_4 as catalyst, gave the ethyl ester 1.38 in high yield.

Due to lack of high pressure facilities, the catalytic hydrogenation of the aromatic ring in 1.38 was accomplished with a rhodium catalyst at 4 atmospheres and 25°C, as an alternative to the original method which used a Raney nickel catalyst at 130 atmospheres and 150°C. However, this alternate procedure did lead to approximately 20% of hydrogenolysed ester 1.67, which was separated from the required hydroxycyclohexyl ester 1.39 by fractional distillation under reduced pressure.

Oxidation of the hydroxyl group in 1.39 was achieved using Jones reagent[15] as an alternative to acidic potassium dichromate as originally reported[5]. The resulting ketone 1.40 was protected as the ketal 1.68, obtained by azeotropic distillation of 1.40 with ethylene glycol and p-TSA in toluene, as in the original method.

Methaminolysis of 1.68 with methylamine in ethanol over several weeks at ambient temperature gave 1.70. Use of sodium methoxide as a catalyst as reported was discontinued as this encouraged hydrolysis to acid 1.69.


HO
CH2CO2R
1.37 R=H
1.38 R=Et
R
R1
CH2CO2Et
1.39 R=H R1=OH
1.67 R=R1=H
1.40 R+R1=O
O
O
CH2R
1.68 R=CO2Et
1.69 R=CO2H
1.70 R=CONHMe
1.71 R=CH2NHMe
1.72 R=CH2NCIMe
1.75
O
H
O
NMe
H
O
+
OH
Cl
NHMe
O
OH
+
MeHN
Cl

SCHEME 1.9 [5]

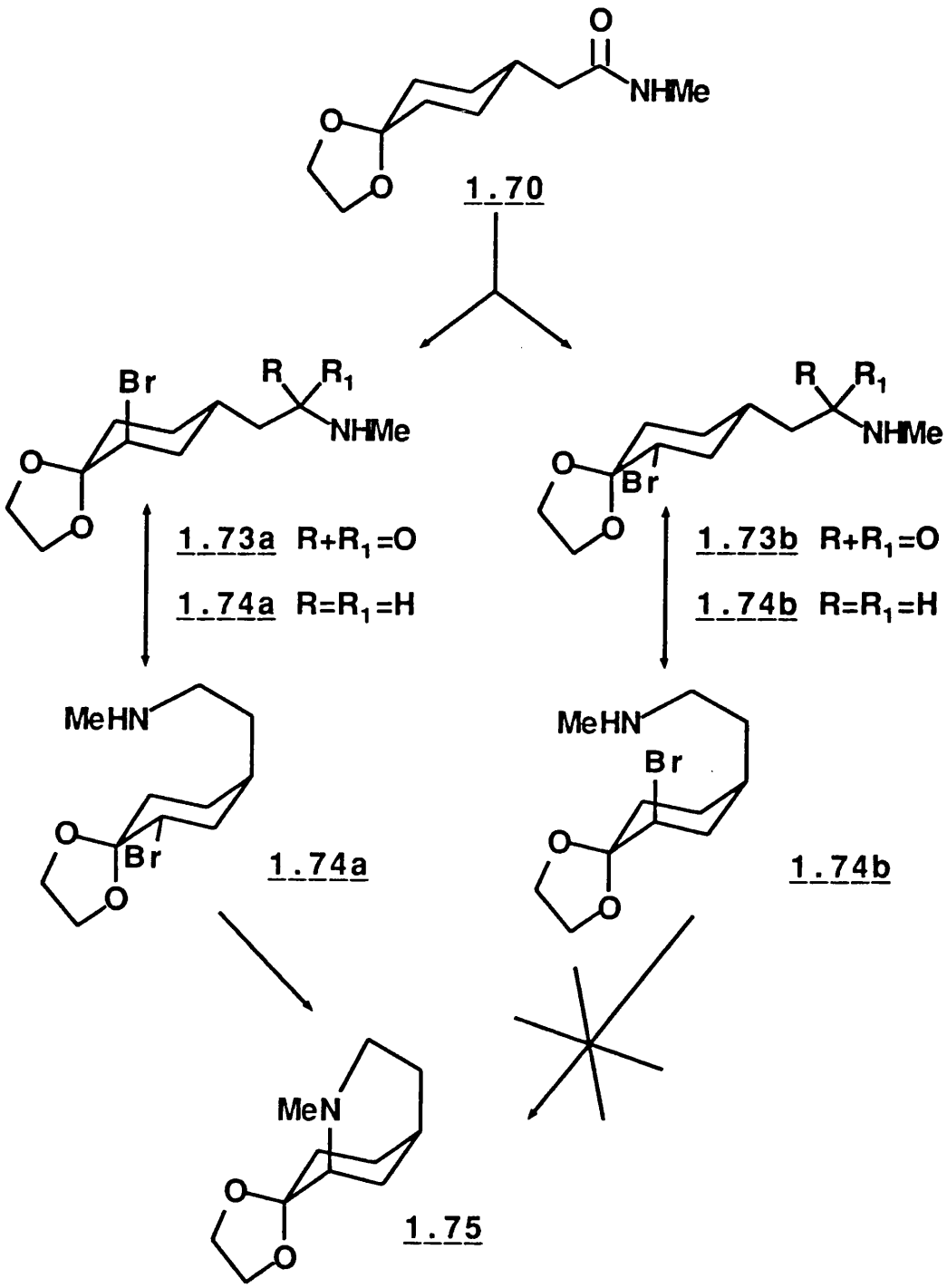
Reduction of the acetoxamide side chain of 1.70 with LAH gave amine 1.71. The N-chloramine 1.72 was obtained quantitatively by treatment of 1.71 with sodium hypochlorite solution. Use of the reported solvolytic techniques for cyclisation of 1.72 (trifluoroacetic acid/methanol) failed to give any cyclic products and resulted only in recovery of 1.71 in poor yield. Repetition of the reaction using trifluoroacetic acid containing traces of water (as suggested by the authors when consulted) gave no improvement.

This stage is elaborated in scheme 1.9.[5]

Synthesis of 1.46 via bromination of 1.70 and subsequent ring closure (scheme 1.10).

Due to the failure of the solvolytic cyclisation of 1.72 (scheme 1.9), the required morphan-8-one 1.46 was obtained by a different route developed in these laboratories (scheme 1.10). The route utilised the amide 1.70 from scheme 1.9 as starting material.

Bromination of 1.70 in ethylene glycol gave a mixture of the 6-bromo trans 1.73a and cis 1.73b isomers. The proportions of each isomer obtained was temperature dependent with 1.73b predominating at ambient temperature (80% @ 20°C). At 55°C, (the maximum temperature before other reactions interfered) the isomers were obtained in approximately equimolar proportions as judged by GLC and ^{1}H NMR. Only the trans isomer 1.73a could ultimately be cyclised (see later) and so the bromination was carried out at 55°C in order to maximise its yield. 1.73a was obtained pure after fractional crystallisation of the isomeric mixture from toluene.


O
NHMe
1.70
Br
R
R1
NHMe
1.73a R+R1=O
1.74a R=R1=H
1.73b R+R1=O
1.74b R=R1=H
MeHN
Br
1.74a
1.74b
MeN
1.75

SCHEME 1.10

Reduction of the amide group in 1.73a with diborane in THF gave amine 1.74a. An aqueous solution of the hydrochloride salt of 1.74a cyclised on treatment with aqueous ammonia to give the cyclic ketal 1.75. Deprotection of 1.75 with aqueous HCl gave the required morphan-8-one 1.46. The overall yield of 1.46 from hydroxyphenylacetic acid was approximately 2%.

This low yield was largely attributable to the stereoselective nature of the cyclisation stage, and the consequent need to separate the isomeric amides 1.73a/b.

The stereochemistry of the brominated intermediates are therefore of interest and will now be discussed with particular reference to their NMR spectra.

Examination of molecular models (see scheme 1.10) showed that the acetoxamide side chain and bromine must be trans for the subsequent cyclisation to occur by the expected SN2 mechanism. The major product from the bromination of 1.70 i.e. 1.73b did not subsequently cyclise and on this basis was assigned the cis configuration. Conversely, 1.73a was assigned the trans configuration.

The observed ^1H NMR spectra of the isomers of 1.73 and 1.74 provided evidence to support these assignments and this evidence will now be presented.

The 400 MHz ^1H NMR spectrum of 1.73a showed the CHBr proton at δ = 4.15 ppm as a narrow quartet with both couplings (to Ha and Hb) 2-3Hz (figure 1.1). This is indicative of an equatorial conformation for CHBr i.e., bromine axial in 1.73a. The 400 MHz ^1H NMR spectrum of 1.73b showed the corresponding CHBr proton at δ~4.2 but obscured, and so no coupling information was available (figure 1.2).

The 60 MHz ^1H NMR spectra of the amines 1.74a/b also provided useful data, in that although the CHBr proton of 1.74b was again obscured at δ = 4.2 (figure 1.4), the corresponding signal in 1.74a occurred at δ = 4.7, which is indicative of an equatorial proton.

Note:- 1.74a has partially cyclised, thus complicating its ^1H NMR (figure 1.3).

Also compare the chemical shift of CHBr in cis and trans-4-tert-butyl-1-bromocyclohexanes[16] (figure 1.5).

FIGURE 1.1

^{1}H 400 MHz NMR SPECTRUM OF 1.73a ($CDCl_3$ solvent, TMS ref.)

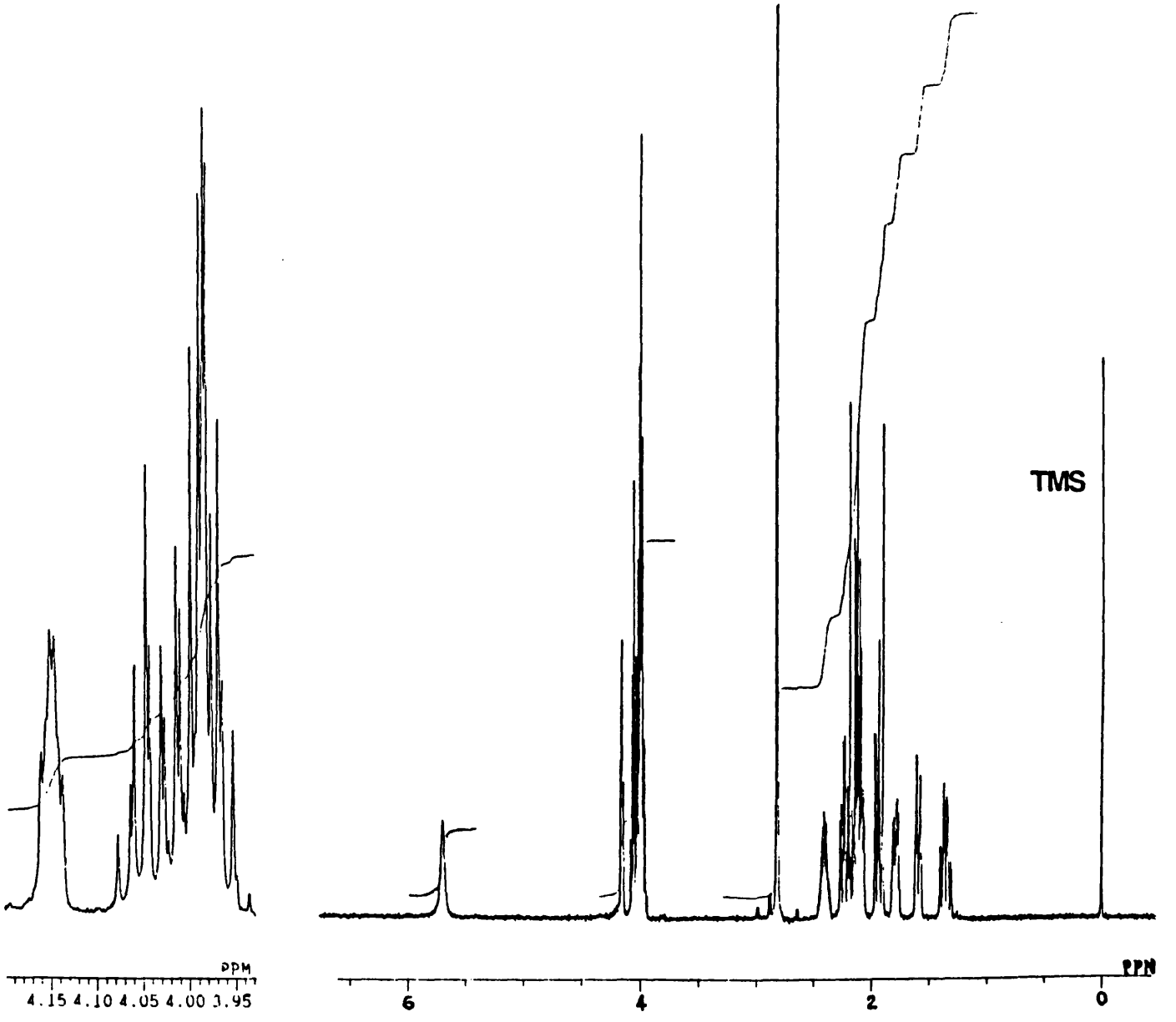


FIGURE 1.2

^{1}H 400 MHz NMR SPECTRUM OF 1.73b ($CDCl_3$ solvent, TMS ref.)

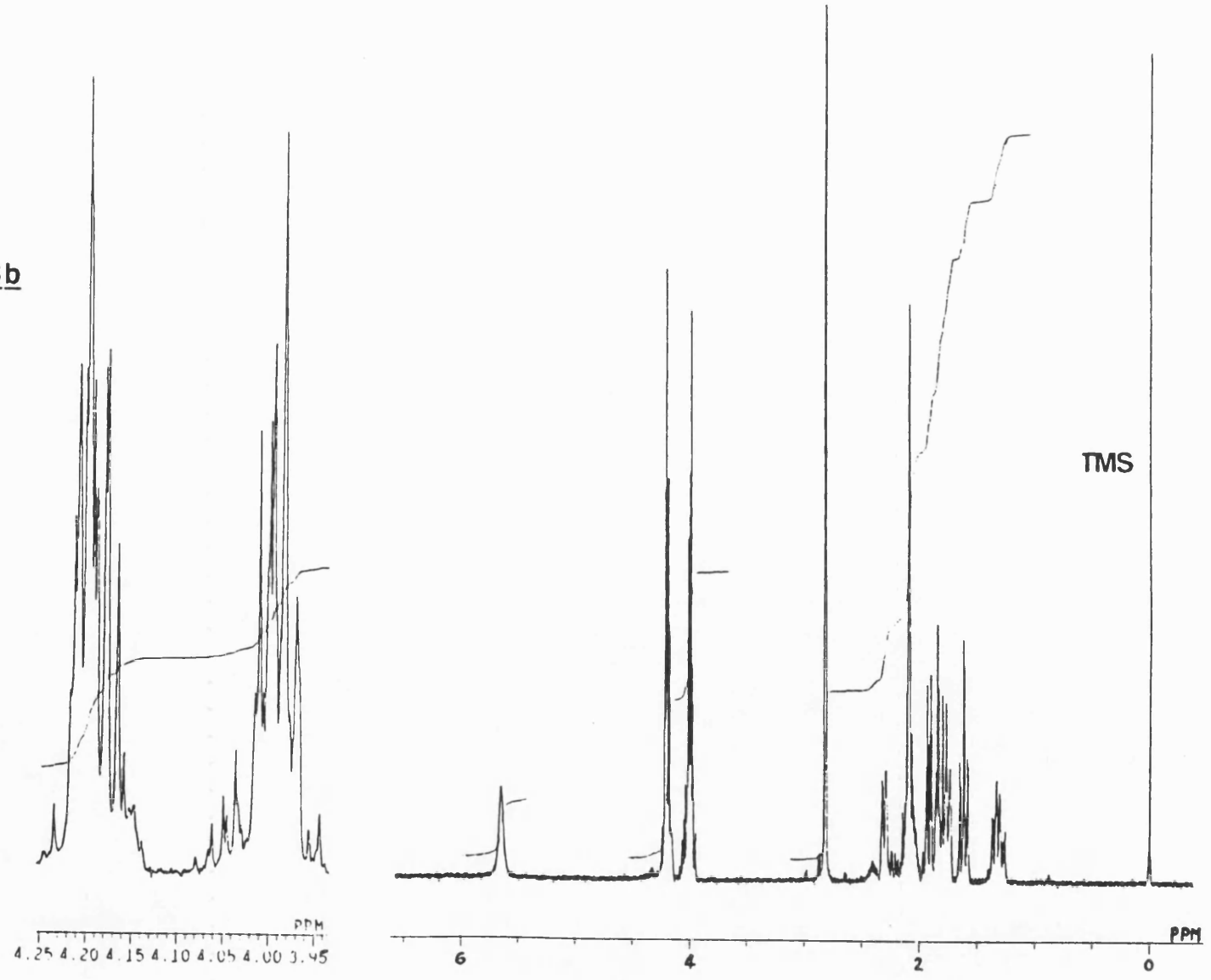


FIGURE 1.3

^{1}H 60 MHz NMR SPECTRUM OF 1.74a ($CDCl_3$ solvent, TMS ref.)

(Note: 1.74a partially cyclised)

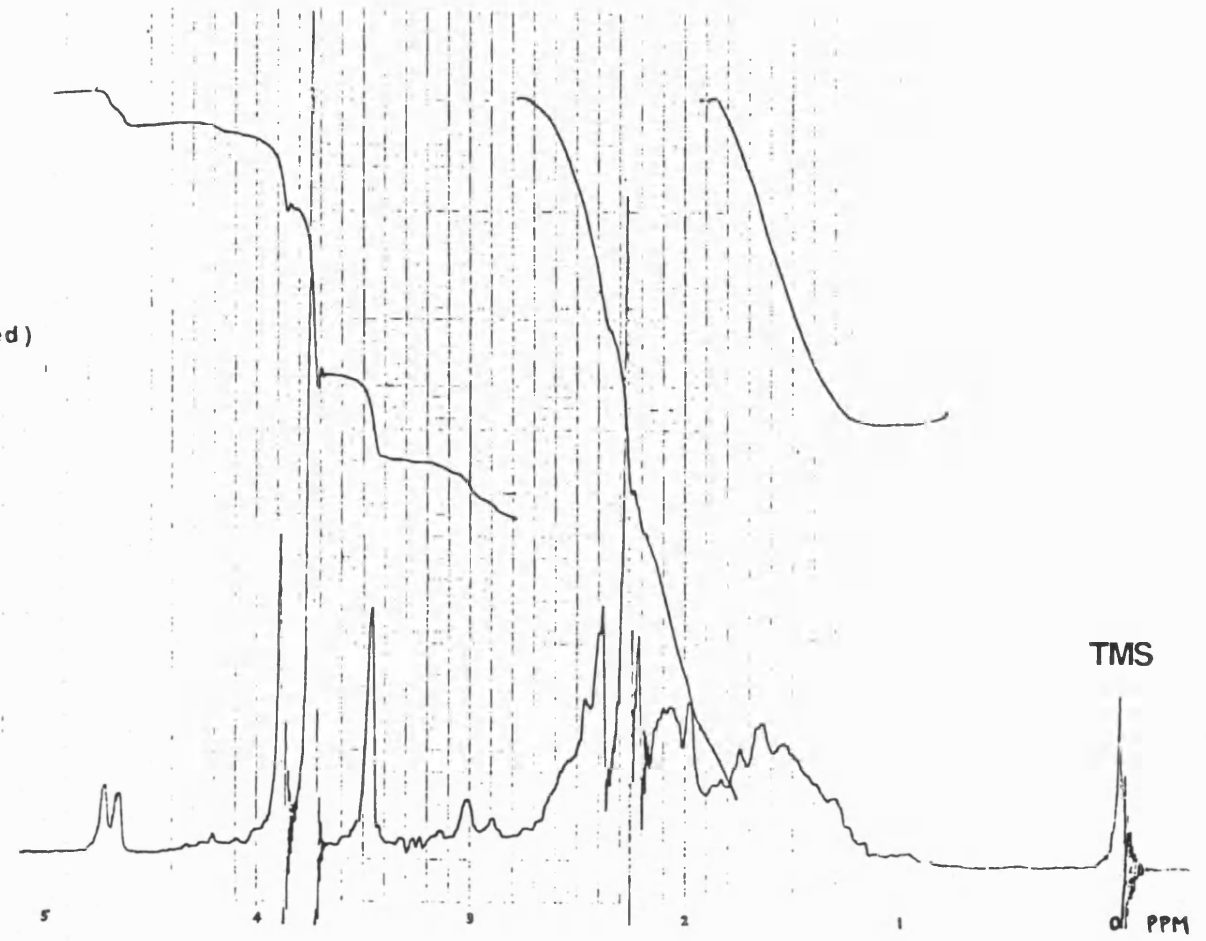
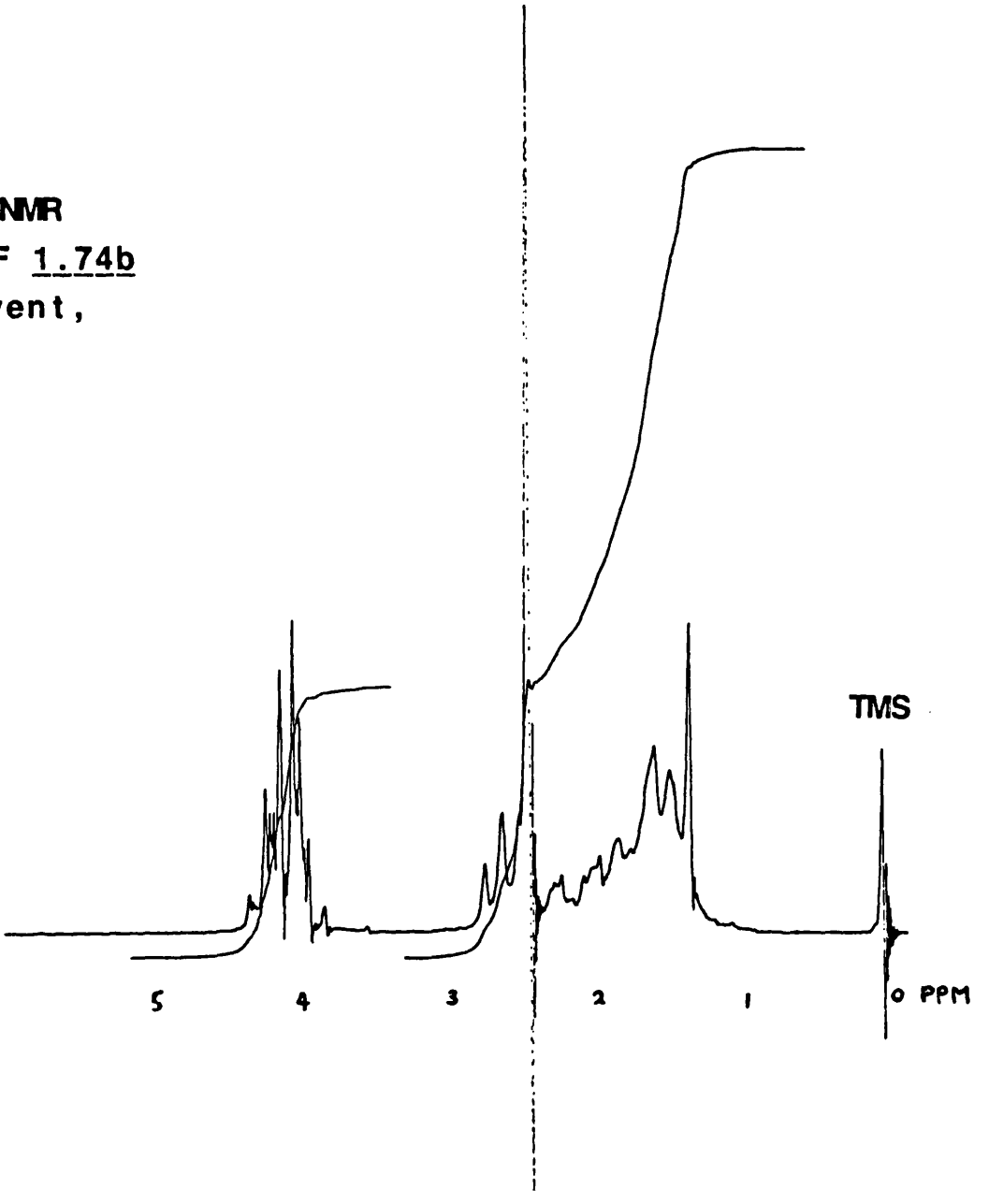
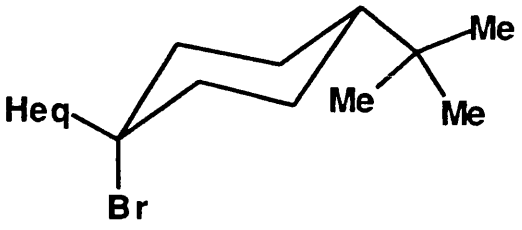
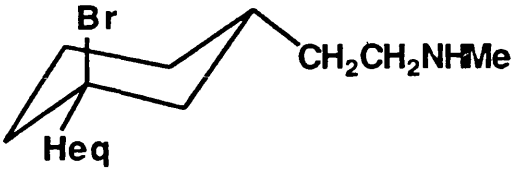


FIGURE 1.4

^{1}H 60 MHz NMR SPECTRUM OF 1.74b ($CDCl_3$ solvent, TMS ref.)





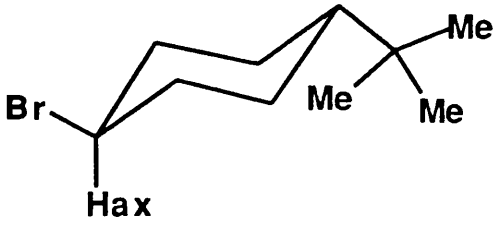


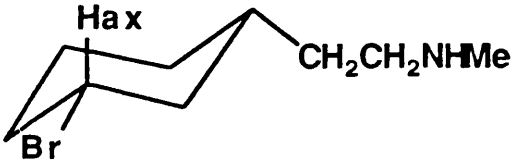
δ (Heq) = 4.63ppm

δ (Heq) = 4.7ppm

cis-4-tert-butyl
-1-bromocyclohexane

1.74a





δ (Hax) = 3.83ppm

δ (Hax) = 4.15ppm

trans-4-tert-butyl
-1-bromocyclohexane

1.74b

FIGURE 1.5

The ^{13}C NMR spectra of 1.73/4a and 1.73/4b were also in accord with these assignments (figure 1.6 and table 1.1) as shown below.

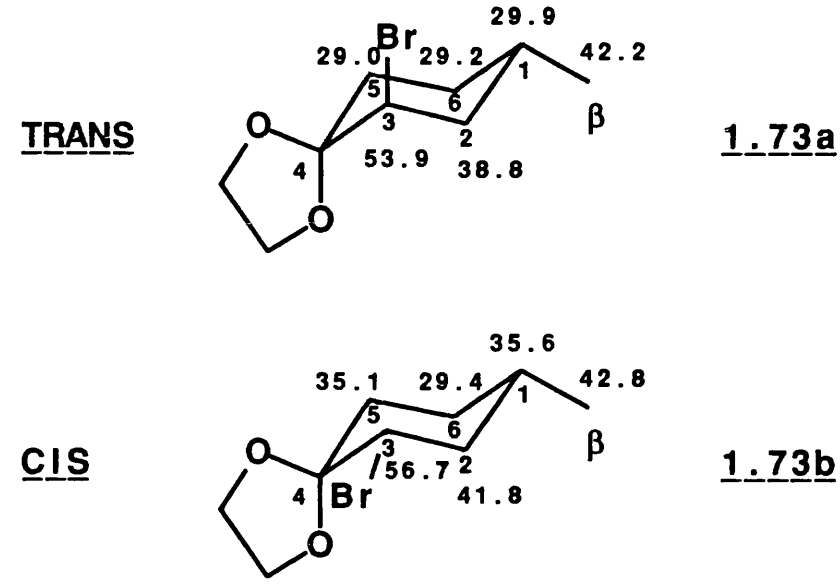
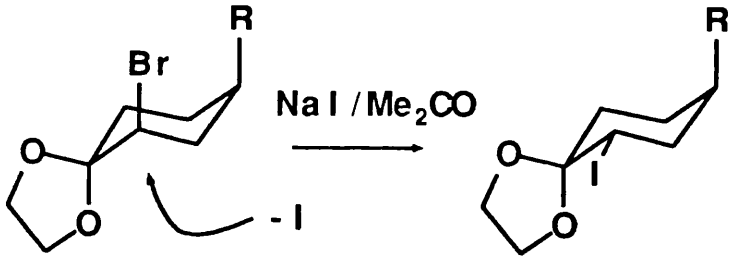


FIGURE 1.6

Note that C-1 and C-5 are sterically compressed by axial bromine[17] in 1.73a, and therefore have higher field chemical shifts than the corresponding carbon atoms in 1.73b (figure 1.6). A similar pattern of shielding of C-1 and C-5 was also observed in 1.74a (table 1.1).

When a mixture of 1.74a and 1.74b were subjected to cyclisation conditions, yields of cyclised product 1.75 were poor. This suggested an interspecies association which precluded the expected cyclisation of 1.74a. It was therefore necessary to separate 1.74a and 1.74b before cyclisation was possible. This was most easily accomplished at the amide stage, i.e. 1.73a/1.73b, as these were solids which could be separated by fractional crystallisation. The amines 1.74a and 1.74b were liquids with similar boiling points. Separation by fractional crystallisation of their hydrochloride or oxalate salts was also attempted without success.

In an attempt to utilise the unwanted isomers 1.73/4b and so synthesise 1.76 the Finklestein halogen exchange process[18] was also unsuccessfully attempted (scheme 1.11).

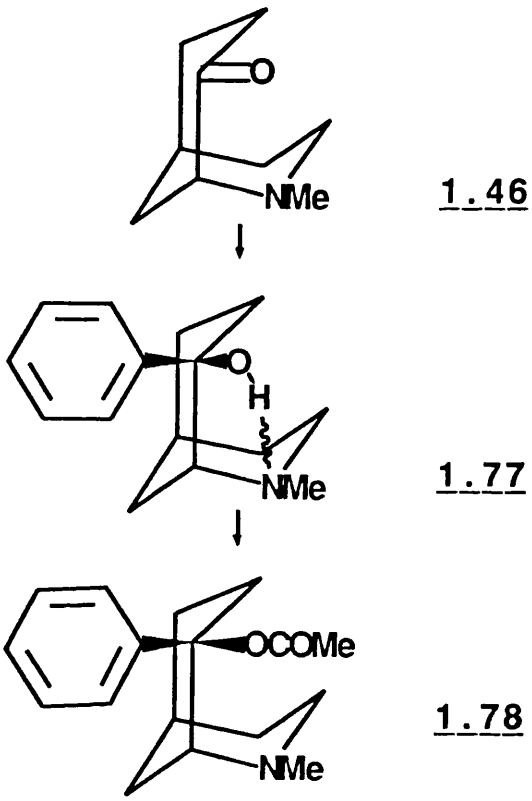


1.73/4b 1.76

SCHEME 1.11 [18]

Having synthesised 2-azabicyclo[3.3.1]non-8-one 1.46, the purpose of the synthesis could be realised, i.e. introduction of an aromatic moiety at position 8.

With this aim, 1.46 was reacted with phenyllithium in anhydrous ether. The alcohol 1.77 was obtained in moderate yield after rigorous purification. IR studies of 1.77 revealed no shift of the O-H band at 3350cm^{-1} on dilution to 0.005M (CCl_4), and no free O-H was detected. This suggested an entirely intramolecularly H-bonded structure (scheme 1.12).



1.46

1.77

1.78

SCHEME 1.12

Acetylation of 1.77 with acetyl chloride and triethylamine in anhydrous ether gave the corresponding ester 1.78. The hydrochloride salt of 1.78 was found to be hygroscopic and could not be obtained pure. However, the oxalate salt was obtained pure and used for biological testing.

Biological Results

N-methyl-8-acetoxy-8-phenyl-2-azabicyclo[3.3.1]nonane oxalate 1.78, was tested for analgesic activity using the mouse hot-plate test (MHP). It was found to be essentially inactive with an ED_{20} of 100mg/kg.

Experimental Section

Infra-red spectra were recorded on a Unicam SP1025 spectrometer.

Melting points (uncorrected) were taken on a Gallenkamp melting point apparatus.

^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer operating at 22.5 MHz. The multiplicity of the resonances was obtained by either off-resonance (partial ^{1}H coupling) spectra, or by INEPT (Insensitive Nuclei Enhanced by Polarisation Transfer) spectra in which the phase of the signal indicated the number of protons attached to each carbon atom.

^{1}H NMR spectra were recorded using JEOL JNM-PMX 60 SI, JEOL PS100 and JEOL GX400 spectrometers. NMR samples (as bases unless stated otherwise) were prepared in 5mm o.d. tubes as approximately 10% solutions in $CDCl_3$ (unless stated otherwise) with TMS as reference.

Mass spectra were recorded on a VG 7070E mass spectrometer operating at 70 eV (EI).

Optical Rotations were measured on an Optical Activity Ltd AA-10 polarimeter.

Elemental analyses were performed by Butterworths Laboratories Ltd., Middlesex.

Formulae and abbreviations as used in the experimental section

$CDCl_3$	Deuterochloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
D_2O	Deuterium Oxide
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
HCl	Hydrochloric Acid
H_2SO_4	Sulphuric Acid
K_2CO_3	Potassium Carbonate
MeOH	Methanol
Me_2CO	Acetone
$MgSO_4$	Magnesium Sulphate (anhydrous)
NaOH	Sodium Hydroxide
Na_2SO_4	Sodium Sulphate (anhydrous)
$NaHCO_3$	Sodium Bicarbonate
Pr^iOH	Isopropanol
THF	Tetrahydrofuran
TMS	Tetramethylsilane

'Solvent was removed' - denotes evaporation under reduced pressure using a rotary evaporator.

Ethyl 4-hydroxyphenyl acetate (1.38)[5]

A stirred mixture of 4-hydroxyphenylacetic acid 1.37 (375 g, 2.47 mol), EtOH (750ml) and concentrated H_2SO_4 (15ml) was heated under reflux for 3 hours, then cooled and solvent removed. The residue was dissolved in water (600 ml) and extracted with Et_2O (5 x 75 ml). The combined organic layers were washed with $NaHCO_3$ solution, dried ($MgSO_4$) and solvent removed to yield crude 1.38 as a yellow oil. Distillation under reduced pressure gave 1.38 (400g, 90%) as a colourless oil, b.p. 127-8°C @ 0.4 mmHg (lit[5] b.p. 138°C @ 0.5mmHg).

^{1}H NMR

1.22 δ (t, J=7 Hz, 3H, CH_3)

3.50 δ (s, 2H, $ArCH_2$)

4.15 δ (q, J=7 Hz, 2H, CH_2)

6.53 δ (br s, 1H, OH, exchanges with D_2O)

6.65 - 7.2 δ (m, 4H, ArH)

Ethyl 4-hydroxycyclohexyl acetate (1.39)[5]

A solution of 1.38 (217g, 1.21 mol) in EtOH (500 ml) was hydrogenated in a Parr apparatus at 60 psi over 5% rhodium on carbon (25g) for 72 hours at 20°C. The mixture was filtered (Celite) and solvent removed to afford a colourless oil,which proved to be a mixture. Distillation under reduced pressure gave 1.39 (160g, 71%) b.p. 115°C @ 0.4 mmHg (lit[5] b.p. 115-6°C @ 0.4mm Hg), and as a forerun, ethyl cyclohexylacetate (1.67; 45g, 22%), b.p. 30-40°C @ 0.4 mmHg (lit[19] b.p. 42-3°C @ 0.2 mmHg), both as colourless oils.

1.39

IR (neat) 1740 cm^{-1} strong (C=O)

3450 cm^{-1} broad (O-H)

^1H NMR 1.24 δ (t, J=7Hz, 3H, CH_3)

1.3 - 2.35 δ (m, 12 aliphatic H with br s at 1.58)

2.42 δ (s, 1H, OH, exchanges with D_2O)

4.13 δ (q, J=7Hz, 2H, CH_2)

(1.67, ^1H NMR as 1.39 excluding O-H signal)

Ethyl 4-oxocyclohexyl^acetate (1.40)[5]

To a stirred solution of 1.39 (100g, 0.54 mol) in Me_2CO (400 ml) was slowly added Jones reagent[15] (made from CrO_3 80.1g, H_2SO_4 69ml, and water 210 ml) keeping the temperature of the reaction mixture less than 20°C with external cooling. The mixture was stirred for a further hour, then the bulk of the Me_2CO removed under reduced pressure and the residual solution extracted with $CHCl_3$ (5 x 200 ml). Drying ($MgSO_4$) and removal of solvent gave a yellow oil. Distillation under reduced pressure gave 1.40, (89g, 90%) as a colourless oil, b.p. 112-5°C @ 1.0 mmHg (lit[5] b.p. 100-115°C @ 1.0 mmHg).

IR (neat) 1730 cm^{-1} strong (C=O)

^1H NMR 1.26 δ (t, J=7Hz, 3H, CH_3)

1.5 - 2.5 δ (m, 11 aliphatic H)

4.16 δ (q, J=7Hz, 2H, CH_2)

Ethyl 1,4-dioxaspiro[4,5]decane-8-acetate (1.68)[5]

A mixture of 1.40 (100g, 0.54 mol), ethylene glycol (55g, 0.9 mol) and p-TSA (2g) in toluene (400 ml) was azeotropically distilled in a Dean-Stark apparatus for 2 hours. The cooled mixture was washed with dilute $NaHCO_3$ solution (3 x 50 ml), brine (3 x 50 ml) and dried (Na_2SO_4). Removal of solvent gave a yellow oil which was distilled under reduced pressure to give 1.68, (110g, 89%) as a colourless oil, b.p. 112-4 @ 0.5mmHg, (lit[5] b.p. 95-8°C @ 0.3mmHg).

IR (neat) 1730 cm^{-1} strong (C=O)

^1H NMR
1.25 δ (t, J=7Hz, 3H, CH_3)
1.5 - 2.4 δ (m, 11 aliphatic H)
3.9 δ (s, 4H, OCH_2CH_2O)
4.1 δ (q, 2H, $C\underline{H}_2CH_3$)

N-Methyl 1,4-dioxaspiro[4,5]decane-8-acetoxamide (1.70)[5]

Methylamine (30g, 1 mol) was condensed into a chilled solution of 1.68 (100g, 0.44 mol) in EtOH (500 ml), stirred at 20°C for 5 weeks with addition of further methylamine as necessary. At the end of this time excess methylamine and solvent were removed to give a solid residue. This crystallised from cyclohexane to give 1.70, (72.5g, 78%) as white flakes, m.p. 109 - 110°C, (lit[5] m.p. 120°C).

IR ($CDCl_3$) 1645 cm^{-1} strong (C=O)
3320 cm^{-1} (N-H)

^1H NMR
1.2 - 2.2 δ (m, 11 aliphatic H)
2.75 δ (d, J=4.5Hz, 3H, NCH_3)

3.91 δ (s, 4H, 2 x CH_2)

6.3 δ (br s 1H, NH, exchanges with D_2O)

^{13}C NMR See table 1.1

8-(N-Methylaminoethyl)-1,4-dioxaspiro[4,5]decane (1.71)[5]

A solution of 1.70 (25g, 0.12 mol) in anhydrous THF (150 ml) was added slowly to a mixture of LAH (10g, 0.25 mol) in anhydrous THF (100 ml), and the mixture refluxed for 16 hours. The mixture was cooled in an ice bath, then 2N NaOH (10 ml) was cautiously added dropwise and the suspension stirred a further 1 hour. Filtration and washing of the cake with CH_2Cl_2 (200 ml), drying ($MgSO_4$), and removal of solvent gave a residue which was distilled under reduced pressure* to give 1.71, (18.4g, 79%) as a colourless oil, b.p. 98°C @ 0.3mmHg, (lit[5] 94-98°C @ 0.3mmHg).

*Tends to polymerise especially at lesser vacuum.

^{1}H NMR 1.1 - 1.9 δ (m, 11 aliphatic H)

2.45 δ (s, 3H, NCH_3)

2.61 δ (t, J=8Hz, 2H, NCH_2)

3.95 δ (s, 4H, OCH_2)

^{13}C NMR See table 1.1

8-(N-Chloro-N-methylaminoethyl)-1,4-dioxaspiro[4,5]decane (1.72)[5]

A mixture of 1.72 (1.0g, 0.005 mol), CH_2Cl_2 (12 ml) and 1M sodium hypochlorite solution (12 ml) was vigorously stirred for 90 minutes at 20°C, in the absence of light. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried (Na_2SO_4) and solvent removed to yield 1.72, (1.1g, 94%) as a pale yellow oil. This was used for the subsequent attempted cyclisation without further purification.

^1H NMR 1.1 - 1.9 δ (m, 11 aliphatic H)
2.94 δ (t, J=8Hz, 2H, NCH_2)
2.96 δ (s, 3H, NCH_3)
3.95 δ (2, 4H, OCH_2CH_2O)

^{13}C NMR See table 1.1

6-Bromo-N-methyl-1,4-dioxaspiro[4,5]decane-8-acetoxamide (1.73)

Bromine (15.1g, 0.094 mol) was added slowly dropwise to a solution of 1.70 (20g, 0.094 mol) in ethylene glycol (400 ml) maintained at 55°C. The mixture was stirred for a further hour then cooled, basified with 2N K_2CO_3 solution and extracted with toluene (5 x 100 ml). Drying (Na_2SO_4) and removal of solvent gave an approximately equimolar mixture of 1.73a/b as a pale yellow solid, (17g, 62%). Repeated crystallisation from toluene gave 1.73b (4.5g, 16%) as white needles, m.p. 152-3°C.

EIMS m/z 292 (M+)

^{1}H NMR 1.3 - 2.5 δ (m, 9 aliphatic H)

2.75 δ (d, J=4.5 Hz, 3H, NCH_3)

3.9 - 4.25 δ (m, 4H, OCH_2CH_2O)

4.15 - 4.25 δ (1H, obscured, CHBr)

6.1 δ (br s, 1H, NH, exchanges with D_2O)

^{13}C NMR See table 1.1

Analysis See table 1.3

Further crystallisation of the combined residues from toluene gave 1.73a (3.9g, 14%) as a white crystalline solid, m.p. 127.5-8.5°C.

EIMS m/z 292 (M+)

^{1}H NMR 1.2 - 2.6 δ (m, 9 aliphatic H)

2.75 δ (d, J=4.5Hz, 3H, NCH_3)

3.95 - 4.05 δ (m, 4H OCH_2CH_2O)

4.15 δ (AB q, J=2.5Hz, CHBr)

6.3 δ (br s, 1H NH, exchanges with D_2O)

^{13}C NMR See table 1.1

Analysis See table 1.3

6-Bromo-8-(N-methylaminoethyl)-1,4-dioxaspiro[4,5]decane (1.74)

To a stirred solution of 1.73a * (1.0g, 0.0034 mol) in anhydrous THF (50 ml), at 0°C, under a nitrogen atmosphere, was added (via syringe), 15 ml of 1M diborane in THF. The resulting solution was refluxed for 5 days, then cooled. Acetic acid (50 ml) was added and the mixture stirred at 20°C for 30 minutes. Solvent was removed, the residue basified with 2N Na_2CO_3, and extracted with EtOAc (3 x 75 ml). The combined organic layers were dried ($MgSO_4$) and solvent removed to give a yellow oil. Distillation under reduced pressure in a Kugel Rohr apparatus gave 1.74a (0.6g, 63%) as a colourless oil, b.p. 125°C @ 0.05 mmHg.

^{1}H NMR 1.1 - 2.7 δ (m, 11 aliphatic H)
2.3 δ (s, 3H, NCH_3)
3.75 δ (s, 4H, OCH_2CH_2O)
3.5 δ (br s, 1H, NH, exchanges with D_2O)
4.7 δ (br d, J= 4 Hz, CHBr)

^{13}C NMR See table 1.1

* 1.73b was similarly reduced to 1.74b, which also had b.p. 125°C @ 0.05 mmHg. (Yield was also comparable to that of 1.74a).

1.74b

^{1}H NMR 1.1 - 2.3 δ (m, 9 aliphatic H)
2.42 δ (s, 3H, NCH_3)
2.58 δ (t, J=7Hz, 2H, NCH_2)
3.9 - 4.25 δ (m, 4H, OCH_2CH_2O)
4.15 δ (1H, obscured, CHBr)

^{13}C NMR See table 1.1

2-Methyl-8-oxo-2-azabicyclo[3,3,1]nonane ethylene ketal (1.75)[5]

To a solution of the hydrochloride salt of 1.74a* (7.0g, 0.022 mol) in water (25 ml) at 0-5°C, was added dropwise, concentrated aqueous ammonia (2.5 ml) over 15 minutes. The solution was stirred for a further hour then extracted with $CHCl_3$ (3 x 25 ml). The combined organic layers were dried ($MgSO_4$) and solvent removed to give a pale yellow oil. Distillation under reduced pressure gave 1.75, (3.7g, 84%) as a colourless oil, b.p. 72°C @ 0.1 mmHg.

EIMS m/z 197 (M+)

^{1}H NMR 1.2 - 2.6 δ (m, 11 aliphatic H)
2.27 δ (s, 3H, NCH_3)
3.05 δ (t, 1H, NCH)
3.9 δ (s, 4H, OCH_2CH_2O)

^{13}C NMR See table 1.2

* The hydrochloride salt of 1.74b consistently failed to give any cyclised products under these conditions. An isomeric mixture of 1.74a/b also failed to yield any significant 1.75 (see discussion).

2-Methyl-2-azabicyclo[3.3.1]non-8-one (1.46)

A solution of 1.75 (3.7g, 0.019 mol) in 30% HCl (25 ml) was stirred at 20°C for 16 hours, then washed with Et_2O (3 x 25 ml), basified with Na_2CO_3 and extracted with $CHCl_3$ (3 x 25 ml). The combined $CHCl_3$ extracts were dried ($MgSO_4$) and solvent removed to give a residual oil. Distillation under reduced pressure gave 1.46, (1.75g, 61%) as a colourless oil, b.p. 72°C @ 0.1 mmHg. The hydrochloride and oxalate salts were found to be hygroscopic and could not be obtained pure.

EIMS m/z 153 (M+)

IR (neat) 1715 cm^{-1} strong (C=O)

^1H NMR 1.3 - 2.7 δ (m, 11 aliphatic H)
2.22 δ (s, 3H, NCH_3)
3.0 δ (t, J=7.5Hz, 1H, CHN)

^{13}C NMR See table 1.2

Analysis See table 1.3

8-Hydroxy-2-methyl-8-phenyl-2-azabicyclo[3,3,1]nonane (1.77)

To a stirred solution of phenyllithium in anhydrous Et_2O (100 ml) made from bromobenzene (2.56g, 0.0164 mol) and lithium (0.23g, 0.0328 mol) and left to react for 1 hour, was slowly added a solution of 1.46 (1.25g, 0.0082 mol) in anhydrous Et_2O (50 ml). The mixture was stirred at 20°C for 1 hour then excess lithium removed and the solution acidified with 2N HCl. The aqueous layer was separated and washed with Et_2O (3 x 50 ml) then basified (K_2CO_3) and extracted with Et_2O (3 x 100 ml). The combined ethereal extracts were dried ($MgSO_4$) and solvent removed to give a viscous orange oil (1.35g). This was chromatographed on silica gel using $CHCl_3$ as eluant to give 1.77, (0.55g, 29%) as a viscous yellow oil which solidified on standing, m.p. 35-40°C.

IR (neat) 3300 cm^{-1} (O-H)

No shift of this band was observed on progressive dilution with carbon tetrachloride (to 0.005M) which indicated an entirely intramolecularly H-bonded structure (scheme 1.12).

^1H NMR

1.2 - 2.6 δ (m, 11 aliphatic H)

2.32 δ (s, 3H, NCH_3)

3.1 - 2.6 δ (m, 1H, NCH)

6.4 δ (br s, 1H, OH, exchanges with D_2O)

6.7 - 7.5 δ (m, 5H, ArH)

^{13}C NMR See table 1.2

8-Acetoxy-2-methyl-8-phenyl-2-azabicyclo[3,3,1]nonane (1.78)

To a solution of 1.77 (0.3g, 0.0013 mol) and freshly distilled triethylamine (0.5g, 0.005 mol) in anhydrous Et_2O (10 ml) was slowly added a solution of freshly distilled acetyl chloride (0.4g, 0.005 mol) in anhydrous Et_2O (5 ml) and the mixture stirred at 20°C for 30 minutes. The precipitated solid was filtered, washed with anhydrous Et_2O (15 ml) and the filtrate evaporated to yield 1.78, (0.025g, 71%) as a viscous yellow oil. The oxalate salt crystallised from EtOH as fine needles (0.21g, 45%), m.p. 163-4°C.

EIMS m/z 273 (M+)

^1H NMR
0.8 - 3.5 δ (m, 12 aliphatic H)
1.97 δ (s, 3H, $COCH_3$)
2.25 δ (s, 3H, NCH_3)
7.1 - 7.5 δ (m, 5H, ArH)

^{13}C NMR See table 1.2

Analysis See table 1.3

TABLE 1.1 ^{13}C NMR DATA ON SOME 8-SUBSTITUTED 1,4-DIOXASPIRO[4,5]DECANES

Compound [a]	C_1	C_2	C_6	C_3 [b]	C_5	C_4	Cα	Cβ	Dioxolane	N-CH_3
1.70	34.0	30.2	30.2	34.4	34.4	108.7	173.1	43.3	64.2	26.1
1.71	34.6	30.3	30.3	34.3[c]	34.3	109.2	50.2	34.6[c]	64.2	36.6
1.72	34.0	30.2	30.2	34.5	34.5	108.9	64.4	34.5	64.2	52.8
1.73a	29.9	38.8	29.2	53.9	29.0	108.0	172.4	42.2	65.0 65.3	26.3
1.73b	35.6	41.8	29.4	56.7	35.1	107.6	172.1	42.2	65.7, 66.1	26.3
1.74a	29.4	42.0	29.9	54.3	2.0	108.0	49.8	39.0	64.7, 64.9	36.6
1.74b	35.5	42.2	29.6	57.4	35.3	107.9	49.7	36.1	65.7, 66.1	36.5

a : Free base in $CDCl_3$ with TMS as reference

b : C3 brominated where appropriate

c : Uncertain assignment

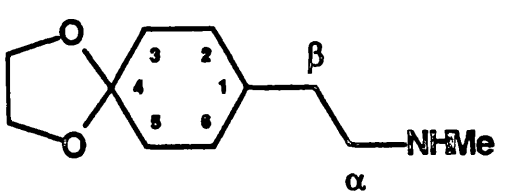
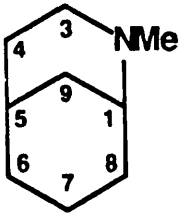


TABLE 1.2 ^{13}C NMR DATA ON SOME 2-AZABICYCLO[3,3,1]NONANES

Compound[a]	C_1	C_3	C_4 C_6 C_7 C_9	C_5	C_8	N-$\underline{C}H_3$	Others		
1.75	64.5	30.2	26.9[b], 28.5[b], 29.7[b], 32.6[b]	36.8	108.9	39.8	63.8, 64.5 (Dioxolane)		
1.46	63.7	30.3	26.7[b], 29.7[b], 35.8[b], 36.6[b]	41.6	212.0	40.4			
1.77	66.0	30.2	26.9[b], 29.1[b], 36.0[b], 38.0[b]	37.4	73.0	40.4	124.4, 126.2, 128.0, 148.8 (Aromatics)		
1.78	64.4	29.0,29.2	26.1[b] 29.3[b], 32.2[b], 37.6[b]	37.4	81.0	22.2	Aromatics 124.6 126.0 128.2 145.5	C = O 170.1	$CO\underline{C}H_3$ 40.5

a Free base in $CDCl_3$ solution with TMS as reference

b Uncertain assignment



Analytical Data Table 1.3

Compound	Formula		C	H	N
1.73a	$C_{11}H_{18}NO_3Br$	Calc	45.25	6.21	4.80
		Found	45.20	6.16	4.64
1.73b	$C_{11}H_{18}NO_3Br$	Calc	45.25	6.21	4.80
		Found	45.19	6.06	4.75
1.46	$C_9H_{15}NO$	Calc	70.55	9.87	9.14
		Found	69.55	10.06	8.97
1.78	$C_{17}H_{24}NO_2.HC_2O_4$	Calc	62.80	6.93	3.85
		Found	62.73	6.99	3.98

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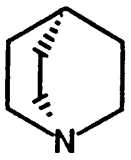
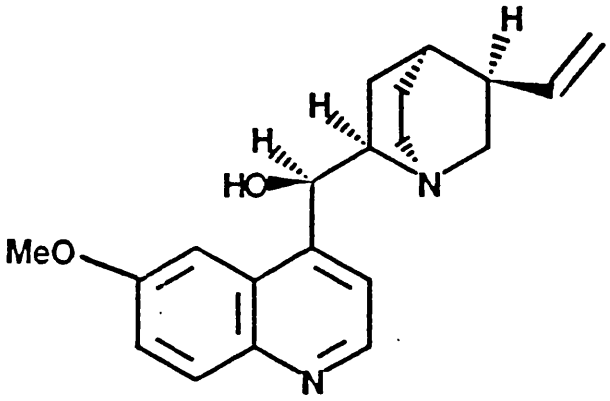
QUINUCLIDINE INTRODUCTION

Quinuclidine is the bicyclic amine 1-azabicyclo[2.2.2]octane 2.1. It is found as an important structural fragment of several alkaloids of the Cinchona group, notably the antimalarial quinine 2.2 as well as cinchonamine 2.3, ajmalidine 2.4 and others.[1,2]



2.1



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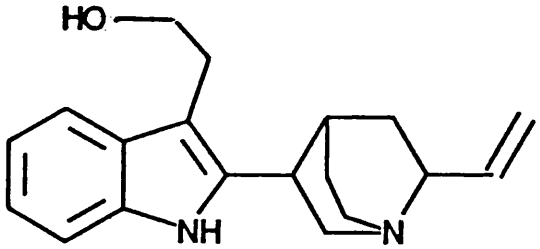

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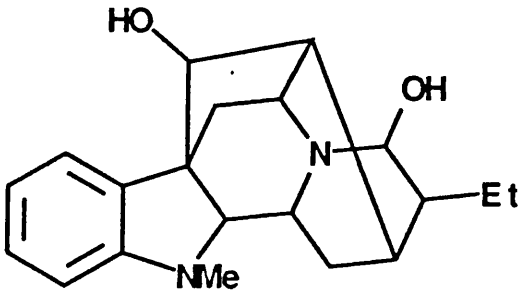
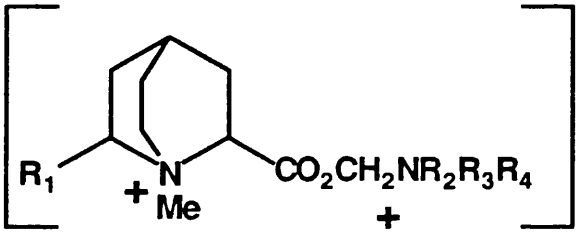


2.4

Several physiologically active synthetic quinuclidine derivatives are in the literature [3-7] and their neurotropic activities have been extensively investigated.[7]

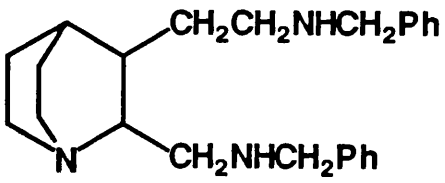
For example, the diquaternary salts dioquin 2.5 and dicoline 2.6 are in clinical use as ganglion blocking agents for the treatment of hypertensive states.



21-

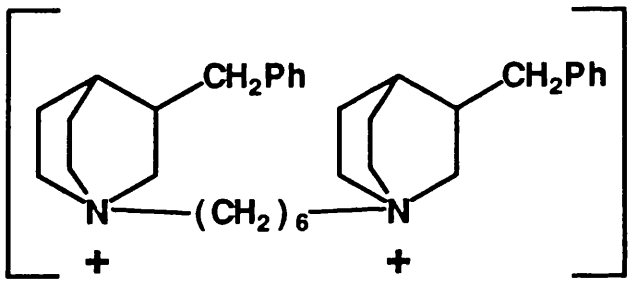
2.5	R_1=H R_2=R_3=Et R_4=Me	DIOQUIN
2.6	R_1=Me R_2=R_3=Et R_4=Me	DICOLINE
2.7	R_1=Me R_2=R_3=R_4=Me	DIMECOLINE

The neurotropic activity of these aminoalkyl esters of quinuclidine-2-carboxylic acid generally perists when the quinuclidine moiety is replaced by the monocyclic piperidine system. However, this is not always the case. For example, in compounds of the type 2.8, replacement of the quinuclidine moiety by acyclic amines leads to loss of neurotropic activity.[1,2]



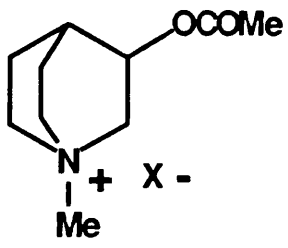
2.8

The most neurotropically active synthetic quinuclidine is qualidyl [8] 2.9, in which two 3-benzylquinucidine molecules are linked symmetrically by an alkyl chain of 6 carbons through the nitrogen atoms.

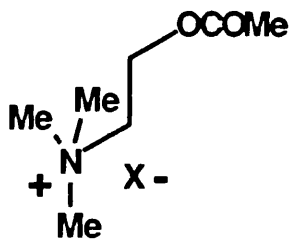


2Cl- 2.9

Some simple esters of 3-hydroxyquinuclidine, for example aceclidine 2.10, also possess neurotropic activity in that they cause the relaxation of smooth muscle tissue. These compounds are thought to act as agonists at acetylcholine muscarinic receptors. The chemical relationship between 2.10 and acetylcholine (2.11) is shown below.



2.10

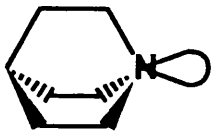


2.11

Aceclidine induces contraction of the pupil of the eye and is used in ophthamology for the treatment of glaucoma, as well as having other surgical uses. [2]

Structure

Quinuclidine has a rigid, fixed structure in which both piperidine rings are held in 'boat' conformations.

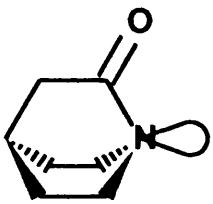


2.1

As a consequence, the lone pair of electrons on the nitrogen atom are virtually unscreened by the adjacent C-H bonds. This endows the quinuclidine molecule with some interesting chemical (and hence biological) features.

For instance, its reactivity with alkyl halides is much greater than that of other simple tertiary aliphatic amines. Quinuclidine reacts with methyl iodide 50 times faster and with isopropyl iodide 700 times faster, than does triethylamine. As a result of this, functionalised quinuclidine derivatives may often have unpredicted chemical properties.

One important example of this is 2-quinuclidinone 2.12 which behaves as an amino ketone rather than as an amide, as might otherwise be expected.



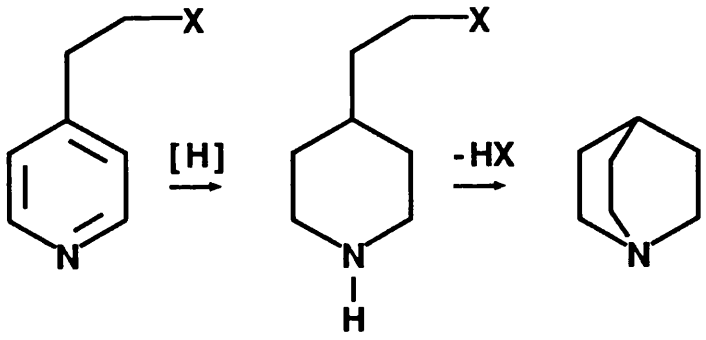
2.12

This property is due to the unfavourable orientation of the nitrogen p orbitals with respect to the carbonyl pi electrons. Conjugation of the type N-C=O <-> $\overset{+}{N}$=C-$\overset{-}{O}$, normal in conventional amides, is impossible in 2-quinuclidones.

2-Quinuclidones are therefore highly basic compared to other amides and are readily protonated. The hydrogen atoms on the carbon atom adjacent to the carbonyl group are acidic, being readily removed by bases, and will also exchange with D_2O. The carbonyl group will also undergo nucleophilic substitution reactions (such as oxime formation), in contrast to carbonyl groups in conventional amides.

Synthesis

There are several methods which have been used for the synthesis of the quinuclidine ring system; these often utilise intramolecular alkylation of haloalkylpiperidine derivatives which are usually obtained by reduction of the corresponding pyridine (scheme 2.1).



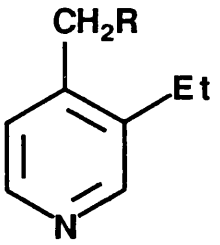
SCHEME 2.1

The first synthetic quinuclidine derivative, 3-ethylquinuclidine 2.17, was prepared in 1904 by Koenigs [9], who utilised this technique for the intramolecular alkylation of 4-(2-iodoethyl)-3-ethylpiperidine 2.16 to achieve quinuclidine ring closure (scheme 2.1a).

Starting from 3-ethyl-4-methylpyridine (2.13), condensation with formaldehyde gave the alcohol 2.14, which was isolated in low yield and subsequently reduced to the piperidine derivative 2.15 using sodium in ethanol. Reaction with HI gave the 4-(iodoethyl) derivative 2.16, which cyclised under the influence of base to give 3-ethylquinuclidine 2.17.

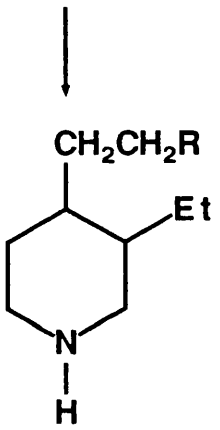
The major disadvantage of Koenigs' synthesis was the extremely low yield (1-2%) of 2.14. However, later workers were able to improve the yield at this stage by the use of paraformaldehyde and higher temperatures. [10]

Similar syntheses were used by later workers [10] to prepare the 4-cyano, 4-bromo and 4-hydroxyquinuclidine derivatives. In these cases, tertiary rather than secondary amines (piperdines) were employed and the appropriate alkyl halide was eliminated from the quaternary salt after cyclisation, by heating under vacuum. For example, in the synthesis of 4-cyanoquinuclidine, 2.21 in scheme 2.2 [11], 4-cyano-1-methylpiperidine 2.18 was used as starting material. Reaction with dichloroethane gave the haloalky/ derivative 2.19. Alkaline intramolecular cyclisation gave the quaternary salt 2.20, which eliminated methyl chloride when heated to 270°C under vacuum and gave 4-cyanoquinuclidine 2.21.



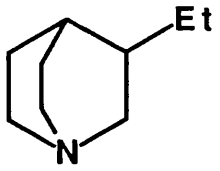
2.13 R=H

2.14 R=CH_2OH



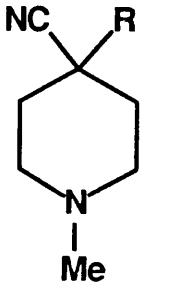
2.15 R=OH

2.16 R= I



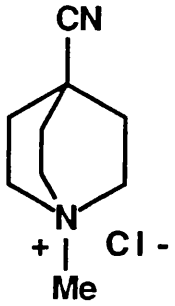
2.17

SCHEME 2.1a [9]

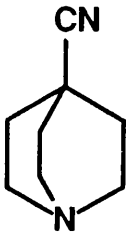


2.18 R=H

2.19 R=CH_2CH_2Cl



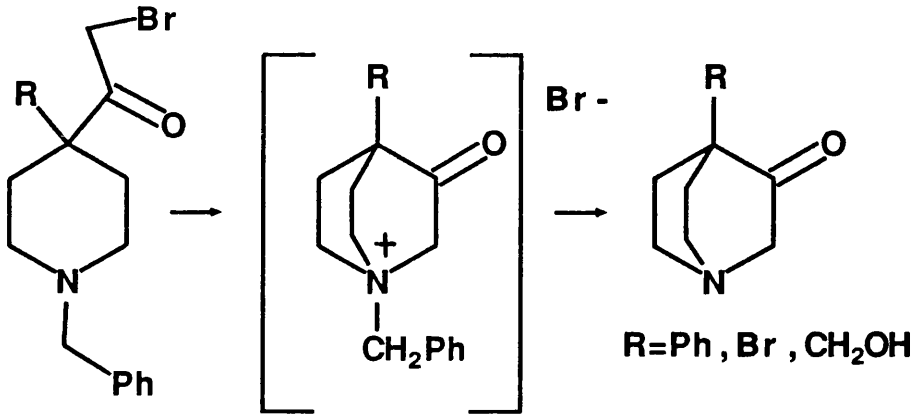
2.20



2.21

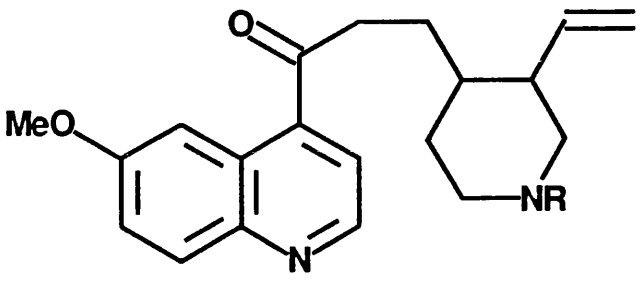
SCHEME 2.2 [11]

In a similar manner to that shown in scheme 2.2, the use of 4-(haloacetyl)-4-substituted-1-benzylpiperidines as starting materials led to 3-oxo-4-substituted quinuclidines. Examples of this type are shown below in scheme 2.3.[12]



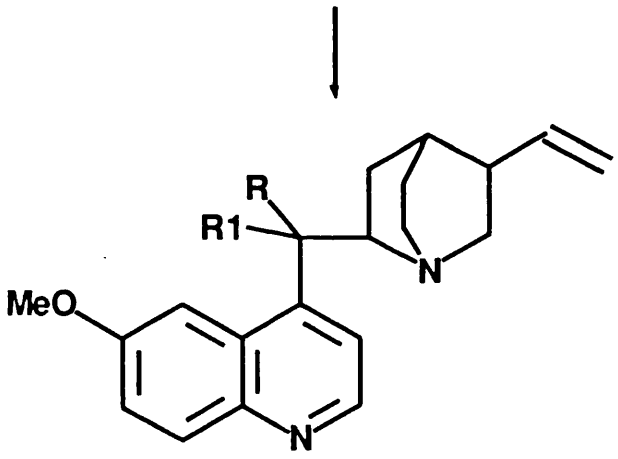
SCHEME 2.3 [12]

In the synthesis of the Cinchona alkaloids a different approach was sometimes required, to avoid the difficulty of halogenation of the oxoalkyl side chain when a vinyl group was also present. This modification involved the synthesis of the N-bromo rather than the appropriate C-bromo intermediate prior to cyclisation. The synthesis of quinine, 2.2 shown in scheme 2.4 [13], is used to illustrate the method. N-Bromination of the starting material 2.22 was achieved with sodium hypobromite. 2.23 was cyclised to ketone 2.24 with alkoxide. The quinine skeleton was obtained by subsequent reduction of 2.24. A number of other Cinchona alkaloids were also prepared using this method.[13]



2.22 R=H

2.23 R=Br

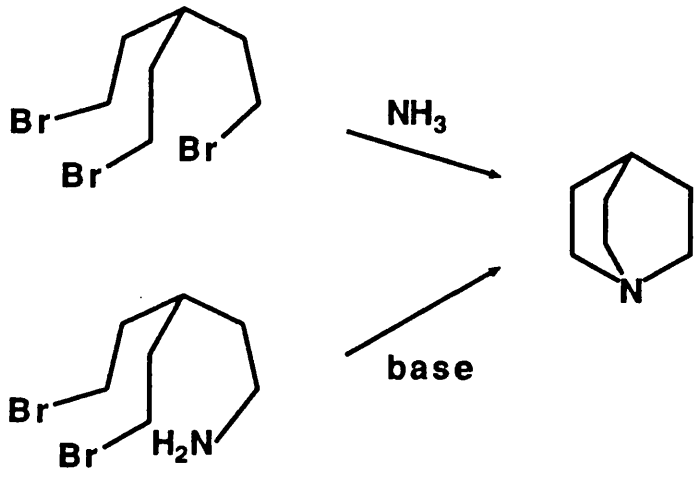


2.24 R+R1=O

2.2 R=H R1=OH
(Quinine skeleton)

SCHEME 2.4 [13]

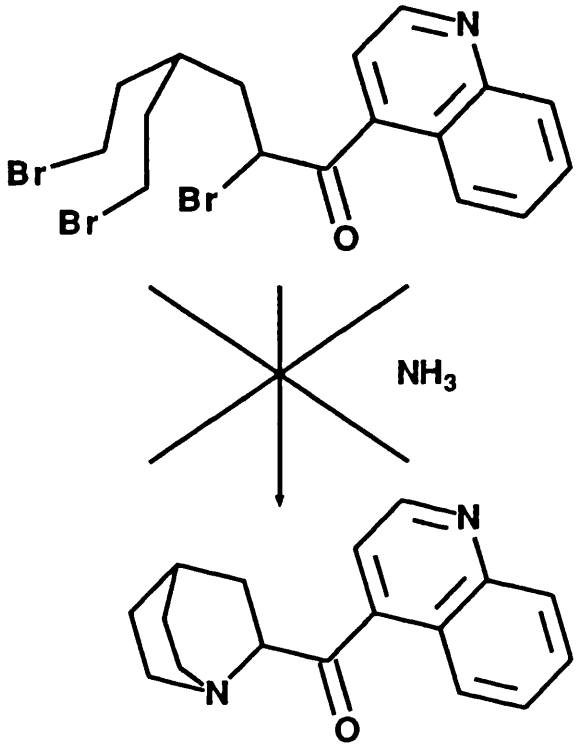
In the 1940s a different approach to the synthesis of quinuclidine derivatives was developed by Prelog.[14,15] There were two variations : 1) the reaction of suitable tribromoalkanes with ammonia under pressure and 2) the double intramolecular alkylation of dibromoalkylamines (scheme 2.5).



SCHEME 2.5

Although these two methods could be used to prepare simple 2 , 3 and 4-alkylated quinuclidine derivatives, they were not universally applicable. For example, they failed when used in an attempted preparation of the quinine analogue 2.25 (scheme 2.5a [16]).

On occasion, either Koenig's or Prelog's method may be used to synthesise a given quinuclidine derivative. This is illustrated for the synthesis of the important intermediate quinuclidine 2-carboxylic acid (2.26 in schemes 2.6 and 2.7).



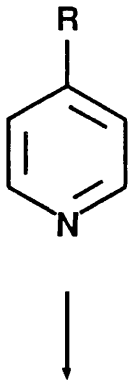
2.25

SCHEME 2.5a [16]

Using Koenig's method (scheme 2.6 [17]) the starting material, 4-methylpyridine 2.27 was oxidised to the 4-formyl derivative 2.28. Condensation of 2.28 with malonic ester gave the 4-(dicarboxyvinyl)pyridine 2.29. The corresponding fully reduced piperdine derivative 2.30 was obtained by hydrogenation of 2.29 over a platinum catalyst. Bromination of 2.30, followed by the usual alkaline intramolecular ring closure gave the 2-(diethoxycarboxyl)quinuclidine 2.32. Hydrolysis and partial decarboxylation gave the required quinuclidine-2-carboxylic acid 2.26.

Prelog's original synthesis of 2.26 in 1937 started with the dichloroethyl ether 2.33 (scheme 2.7 [18]). Reaction with malonic ester gave the diester 2.34. Hydrolysis, partial decarboxylation and re-esterification of the remaining carboxyl group in 2.35 gave mono-ester 2.36. Reduction of 2.36 with sodium in ethanol gave the alcohol 2.37, which was converted to the corresponding bromide 2.38. This reacted with malonic ester to give 2.39. Hydrolysis and partial decarboxylation gave the mono-acid 2.40. Opening of the pyran ring of 2.40 with HBr under pressure gave 2.41 which was then brominated α to the carboxyl group. The resulting tribrominated derivative 2.42 cyclised on treatment with ammonia under pressure to give quinuclidine-2-carboxylic acid 2.26. The overall yield was 4%.

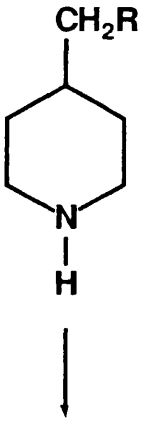
Quinuclidine-2-carboxylic acid is an extremely useful starting material for the synthesis of many other 2-substituted quinuclidine derivatives. Some of these possible transformations are illustrated in scheme 2.8.



2.27 R=Me

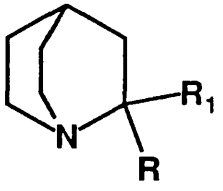
2.28 R=CHO

2.29 R=CHCH(CO_2Et)$_2$



2.30 R=CH(CO_2Et)$_2$

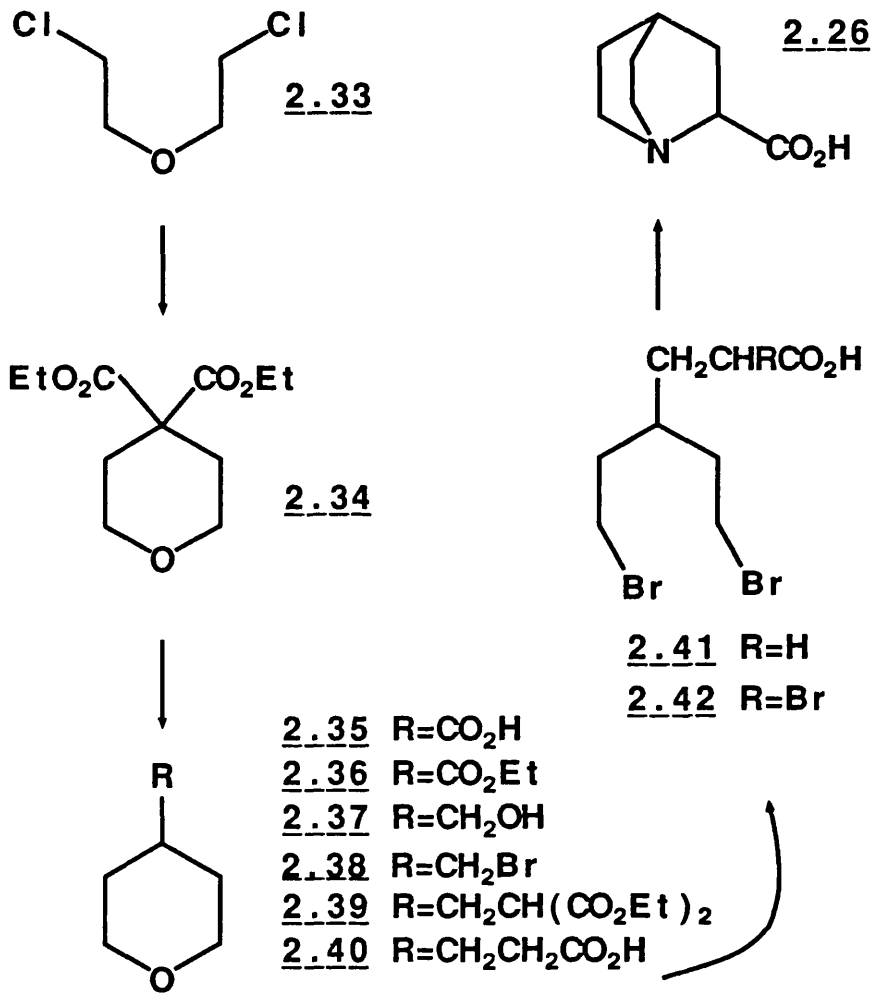
2.31 R=CBr(CO_2Et)$_2$



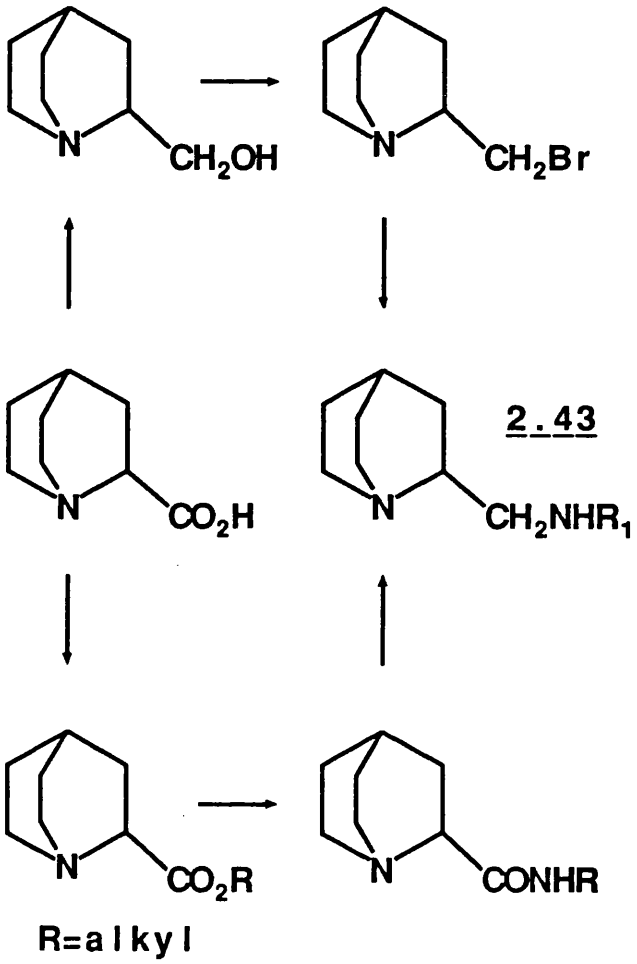
2.32 R=R_1=CO_2Et

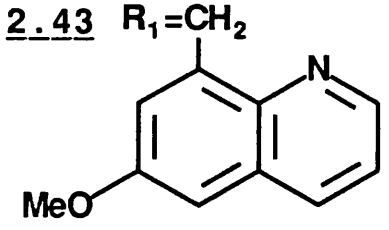
2.26 R=H R_1=CO_2H

SCHEME 2.6 [17]


Cl
Cl
O
2.33
2.26
N
CO2H
EtO2C
CO2Et
O
2.34
CH2CHRCO2H
Br
Br
2.41 R=H
2.42 R=Br
R
O
2.35 R=CO2H
2.36 R=CO2Et
2.37 R=CH2OH
2.38 R=CH2Br
2.39 R=CH2CH(CO2Et)2
2.40 R=CH2CH2CO2H

SCHEME 2.7 [18]





(QUININE ANALOGUE)

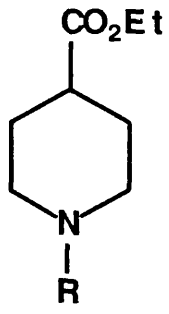
SCHEME 2.8 [2]

Another versatile quinuclidine derivative which has been widely used for the preparation of many 3 and 2,3 substituted quinuclidines is 3-quinuclidone 2.44, first prepared by Clemo and Metcalfe in 1937. [19]

Starting from ethyl isonipecotinate (2.45 in scheme 2.9), reaction with ethyl chloroacetate gave the diester 2.46. Cyclisation of 2.46 with potassium in toluene, followed by saponification of the resulting quinuclidine ester 2.47 and decarboxylation of the resulting acid 2.48 led to 3-quinuclidone 2.44. Other workers subsequently modified and improved the synthesis. For example, potassium tert-butoxide could be substituted for metallic potassium at the cyclisation stage to give a greatly improved yield. [20]

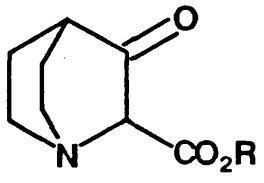
Some of the many 3 substituted and 2,3 disubstituted quinuclidine derivatives which may be prepared from 3-quinuclidone are illustrated in scheme 2.10.

Some of these transformations were utilised for the preparation of potentially active derivatives (see discussion).



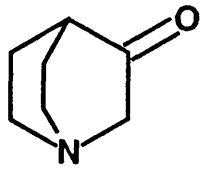
2.45 R=H

2.46 R=CH_2CO_2Et



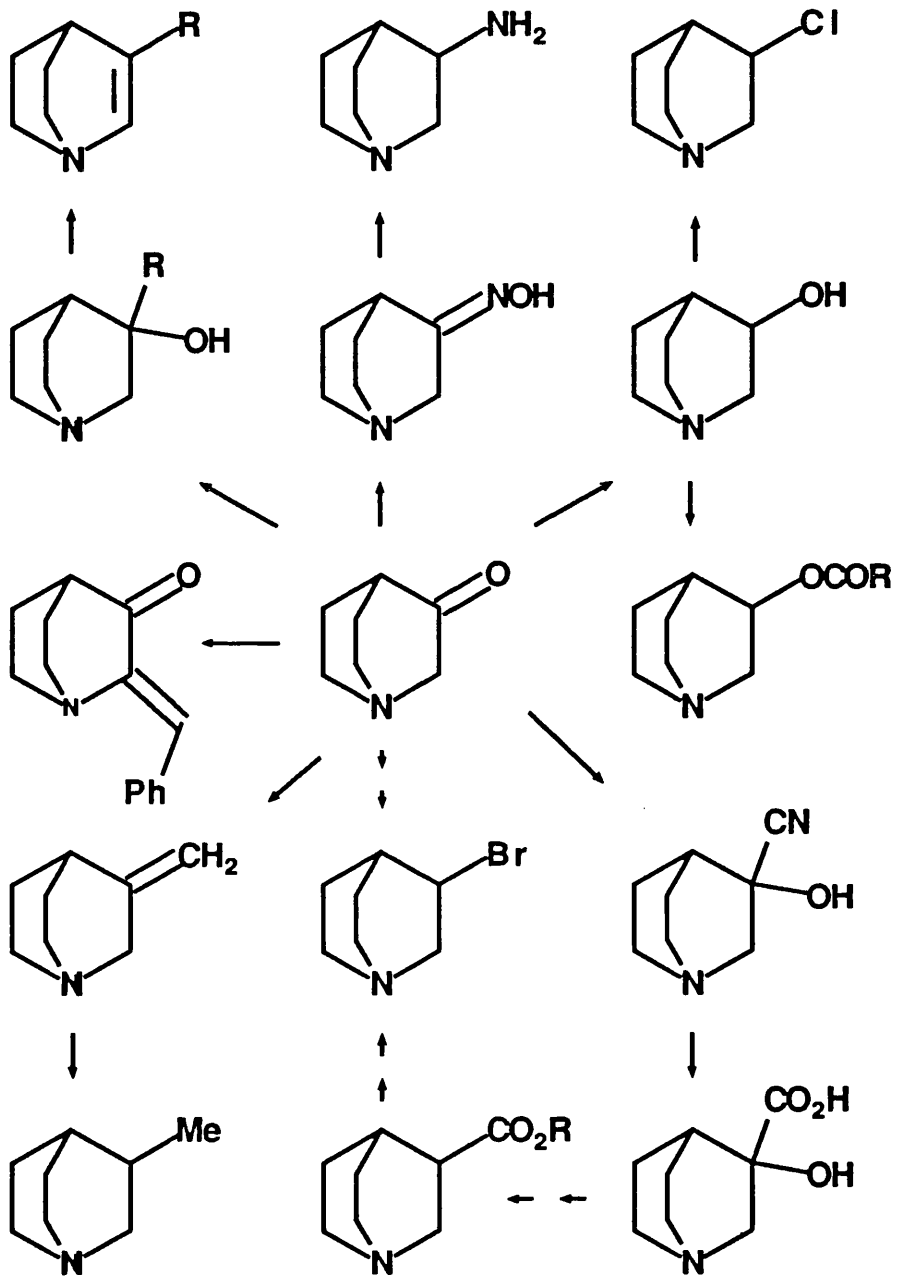
2.47 R=Et

2.48 R=H



2.44

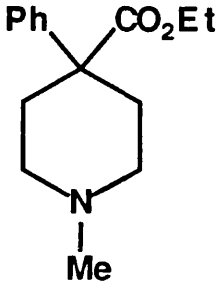
SCHEME 2.9 [19]



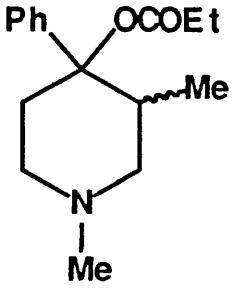
SCHEME 2.10

QUINUCLIDINE DISCUSSION

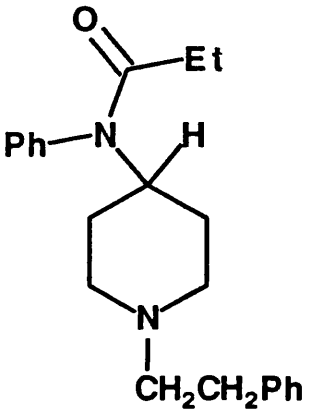
4-Arylpiperidine based narcotic analgesics are an important class of drugs for the treatment of chronic pain. Pethidine 2.49, its 3-methyl reversed ester derivatives (prodines) 2.50 and fentanyl 2.51 are well known examples.



2.49

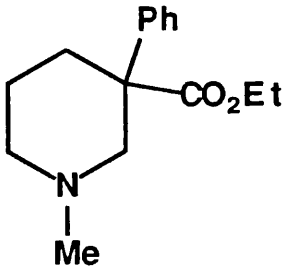


2.50

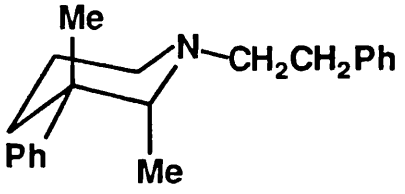


2.51

Several 3-arylpiperidines have been reported, for example β-pethidine 2.52 is approximately one half as active as pethidine. [22] Others in this class also retain analgesic properties, albeit at a lower level than their 4-aryl counterparts.



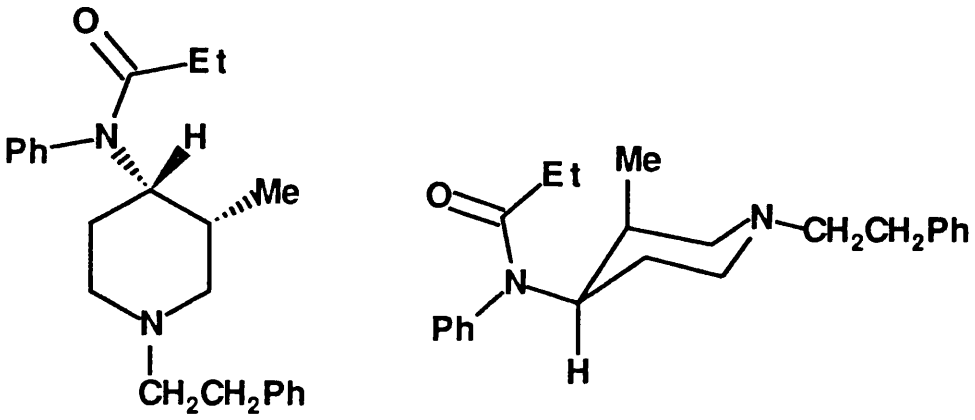
2.52



2.53

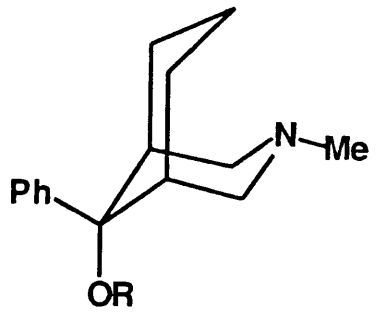
The single isomeric form of the 3-arylpiperidine derivative tentatively assigned the configuration represented by 2.53 is one exception, showing analgesic activity several times that of pethidine in rodent tests.[21]

Fentanyl 2.51 is a 4-anilinopiperidine analogue of pethidine and is a highly potent, short acting analgesic which has been used in clinical practice over the last 20 years.[23] The stereochemical structure activity relationships of fentanyl derivatives largely follow those in the pethidine and prodine series. Thus cis-3-methylfentanyl, 2.54, is 8 times more active than fentanyl itself.[24,25]



2.54

Constrained analogues of piperidine-based analgesics have also been reported and certain of these have proved potent in rodent tests. For example, the two 3-azabicyclo[3,3,1]nonane derivatives 2.55 - 2.57 exhibit a higher level of analgesic potency than pethidine itself and may be considered as a class of 3,5-trimethylene bridged 4-arylpiperidines.[26]



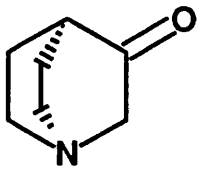
2.55 R=Me

2.56 R=Et

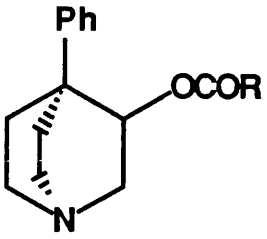
2.57 R=COEt

Quinuclidines are a further class of sterically constrained piperidine derivatives and although many quinuclidines exhibit various neurotropic actions, few have been examined for analgesic activity.

In 1957, a series of 4-phenyl-3-acyloxyquinuclidines of the type 2.58 were examined but few analgesic properties were found.[12]



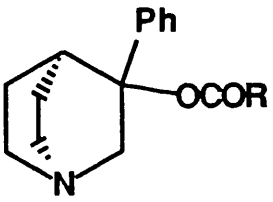
2.44



2.58

Quinuclidine analogues of prodine and fentanyl should be readily accessible via 3-quinuclidone 2.44. Reaction of 2.44 with Grignard or similar reagents should lead to 3-arylprodine analogues of the type 2.59.

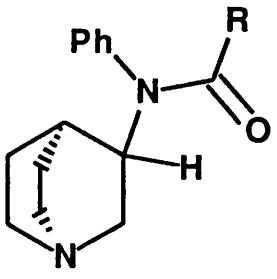
2.44 $\xrightarrow[(RCO)_2O]{PhMgX}$



2.59

Similarly, quinuclidine analogues of fentanyl such as 2.60 should be accessible by condensation of 2.44 with aromatic amines.

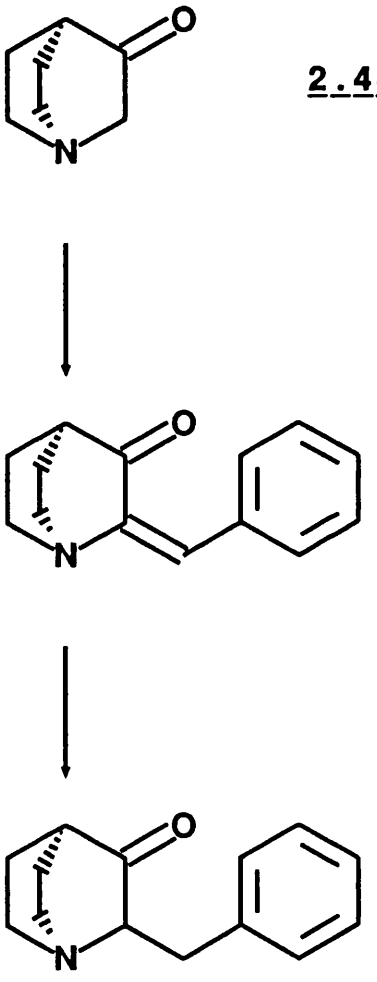
2.44 $\xrightarrow[[H]]{PhNH_2}$ $(RCO)_2O$



2.60

Variation of the N-substituent plays an important role in the determination of the type and magnitude of analgesic action in all classes of narcotic analgesics. Typical examples in morphinoid systems are N-alkyl and N-cyclopropylmethyl (CPM) which confer antagonist properties on the derivative, and N-phenethyl, which tends to increase agonist activity. In the prodine and other piperidine based classes of narcotic analgesics, N-alkyl and N-CPM derivatives generally behave as agonists and show few antagonist properties [27], whilst the N-phenethyl substituent is important to the high potency of fentanyl.

Due to the tertiary nitrogen atom in the quinuclidine system, it is not possible to directly introduce substituents on nitrogen without quaternisation. However, 2-benzyl derivatives are accessible via condensation of 2.44 with benzaldehyde (Claisen-Schmidt), followed by reduction of the benzylidene double bond [4] (scheme 2.11).



2.44

2.54

2.55

SCHEME 2.11 [4]

The 2-benzylquinuclidines accessible from 2.55 by Grignard reactions or by condensation with aromatic amines might then be considered as constrained N-phenethyl analogues of their piperidone counterparts (figure 2.1).

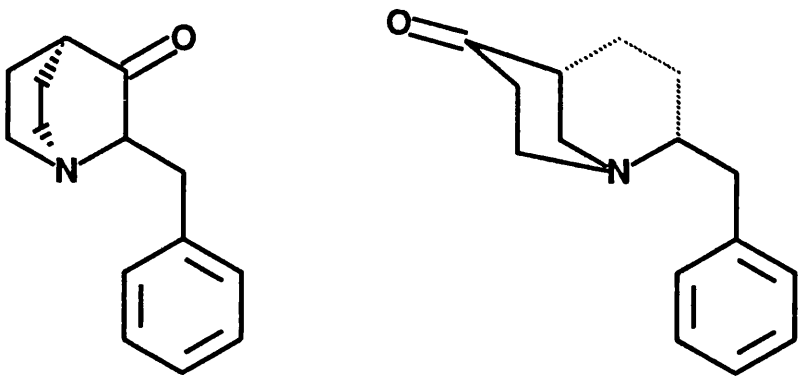


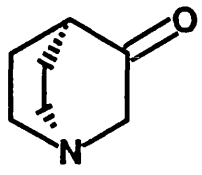
FIGURE 2.1

In the present work, several derivatives of 2-benzylquinuclidine have been prepared in the analogues of the prodine and fentanyl series.

Chemistry

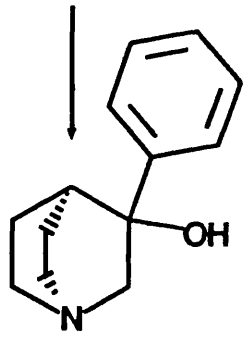
Quinuclidine Analogues of Prodine (Scheme 2.12)

Reaction of 3-quinuclidone with phenylmagnesium bromide in anhydrous THF gave the alcohol 2.61. Subsequent treatment with acetic and propionic anhydride gave the esters 2.62 and 2.63 respectively (scheme 2.12).

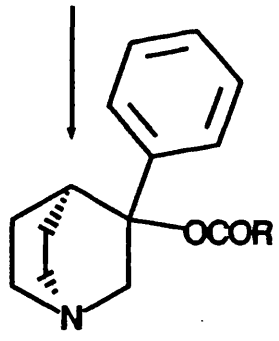


2.44

(ex ALDRICH CHEM CO.)



2.61



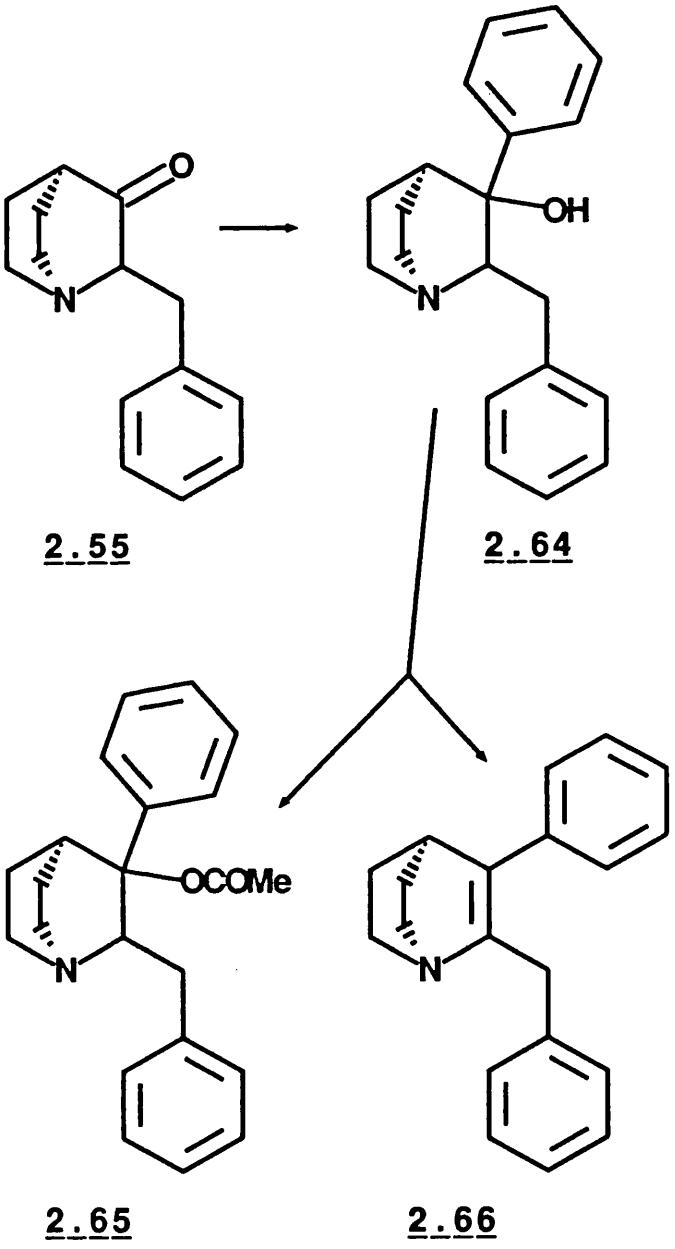
2.62 R=Me

2.63 R=Et

SCHEME 2.12

2-Benzylquinuclidine Analogues of Prodine (Scheme 2.13)

Firstly, reaction of 3-quinuclidone 2.44 with benzaldehyde in the presence of base gave 2-benzylidene-3-quinuclidone 2.54 (scheme 2.11 [4]). Reduction of the double bond with H_2 over Adams catalyst gave 2-benzyl-3-quinuclidone 2.55.[28] Compound 2.55 reacted with an excess of phenyllithium in anhydrous ether to give 2-benzyl-3-hydroxy-3-phenylquinuclidine 2.64. Attempts to react 2.64 directly with acetyl chloride or acetic anhydride led to appreciable dehydration and poor conversion to the required ester 2.65. Substantially improved conversion to 2.65 was initially achieved by *in situ* decomposition of the organolithium complex of 2.64 directly with acetic anhydride. After 'normal' work up, a mixture of unreacted alcohol 2.64, ester 2.65 and 2-benzyl-3-phenyl-Δ 2,3-quinuclidene 2.66 was obtained in an approximate ratio of 2 : 3 : 1 as measured by GLC analysis (area %). Chromatography of this mixture on silica gel gave pure 2.66 in low yield, plus a further mixture which was converted to the oxalate salt. Crystallisation from acetone and subsequent liberation of the free base gave pure ester 2.65. This was a single isomer as judged by ^{13}C NMR spectroscopy (figure 2.2). Examination of molecular models showed the configuration with aromatic substituents *trans* (2.65a) to be sterically favoured (figure 2.3) and thus to be the most likely product.

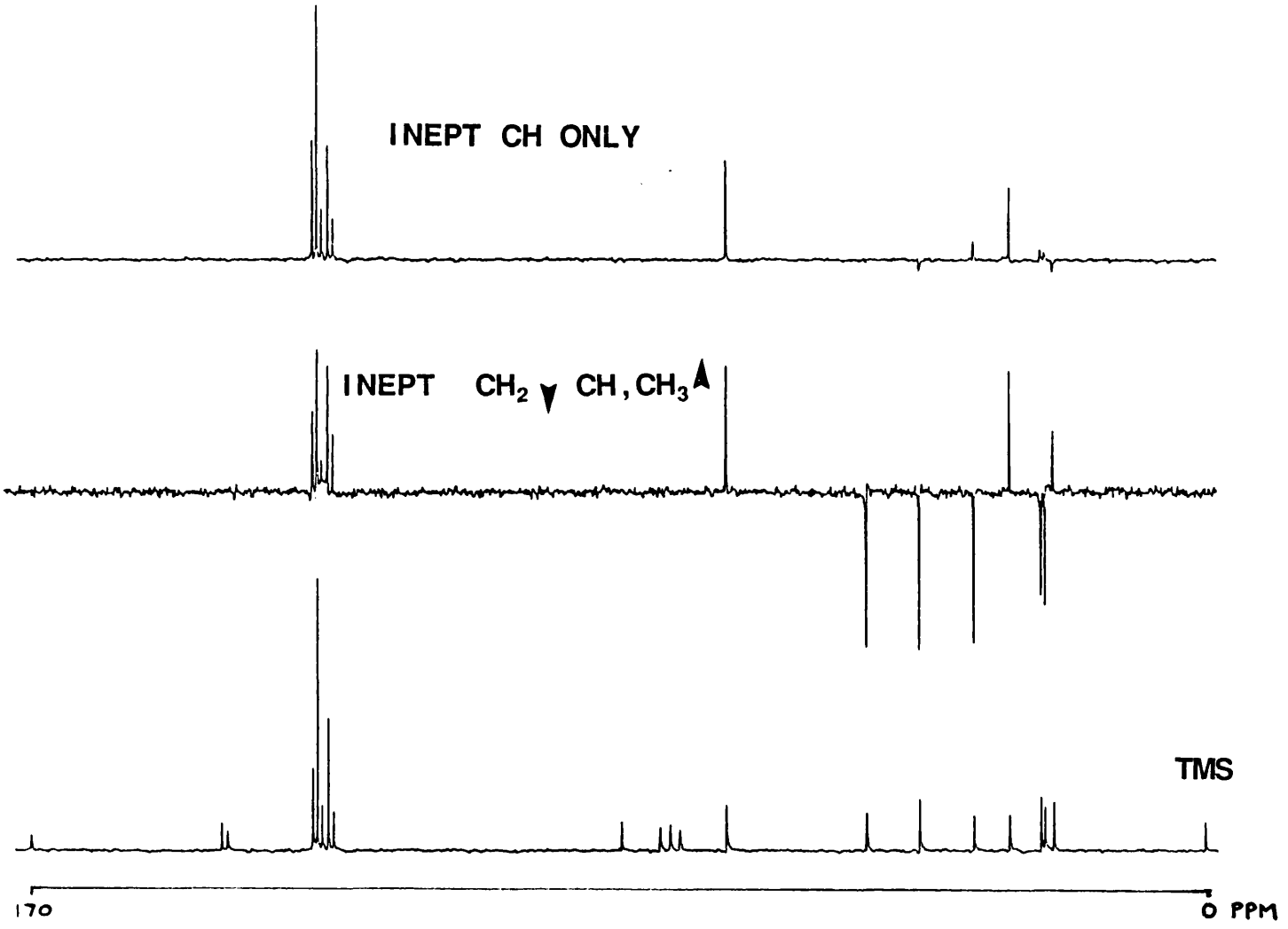


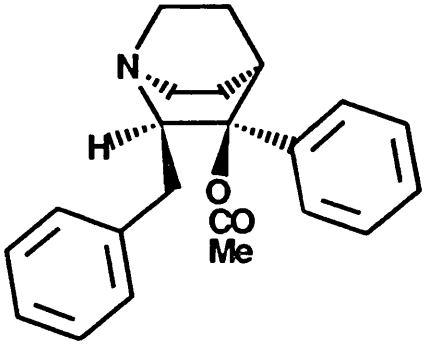
2.55 2.64 2.65 2.66

SCHEME 2.13

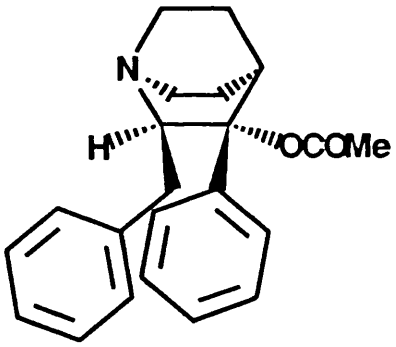
FIGURE 2.2

^{13}C 22.5 MHz NMR SPECTRUM OF 2.65 ($CDCl_3$ solvent, TMS ref.)





2.65a



2.65b

FIGURE 2.3

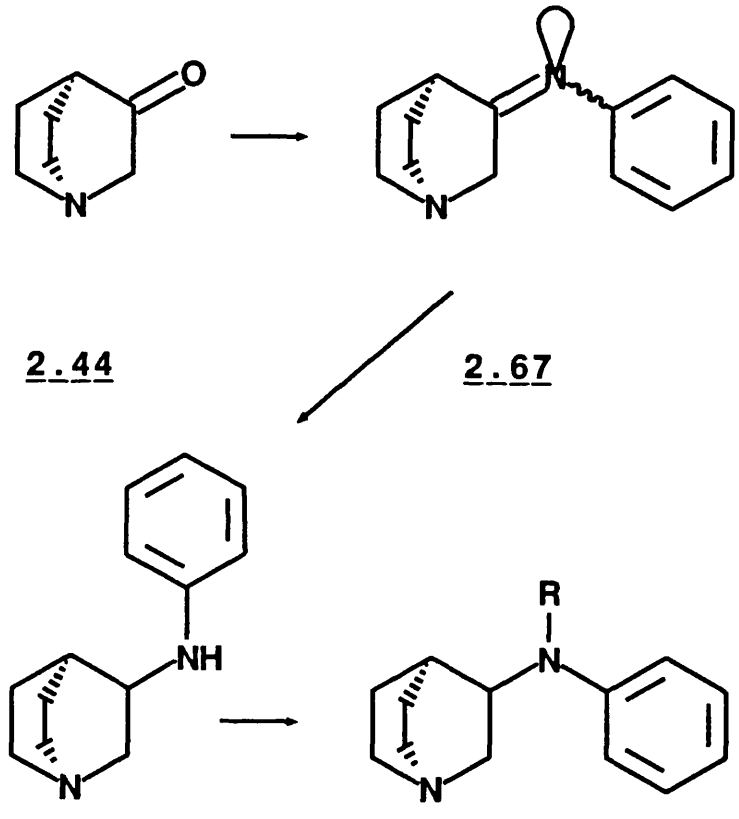
Quinuclidine Analogues of Fentanyl (Scheme 2.14)

Condensation of 3-quinuclidone 2.44 with aniline in toluene using zinc chloride as catalyst, gave the anil 2.67. This was shown to be an approximately equimolar mixture of cis and trans isomers by ^{13}C NMR (figure 2.4). Reduction of 2.67 with LAH in THF gave the amine 2.68. Heating with the appropriate anhydride gave the N-acetoxy and N-propionoxy amides 2.69 and 2.70 respectively.

Reduction of 2.70 with LAH gave the N-propyl derivative 2.71.

2-Benzylquinuclidine Analogues of Fentanyl (Scheme 2.15)

Condensation of 2-benzyl-3-quinuclidone 2.55 with aniline in toluene as before gave the anil 2.72. In contrast to the unsubstituted anil 2.67, 2.72 was shown to be a single isomer by ^{13}C NMR (figure 2.5). Steric interference of the 2 aromatic rings probably precluded the formation of isomer 2.72b (figure 2.6) and also explained the extended reaction time (6 days) and poor yield of the condensation (see experimental section).



2.44 2.67

2.68

2.69 R=COMe

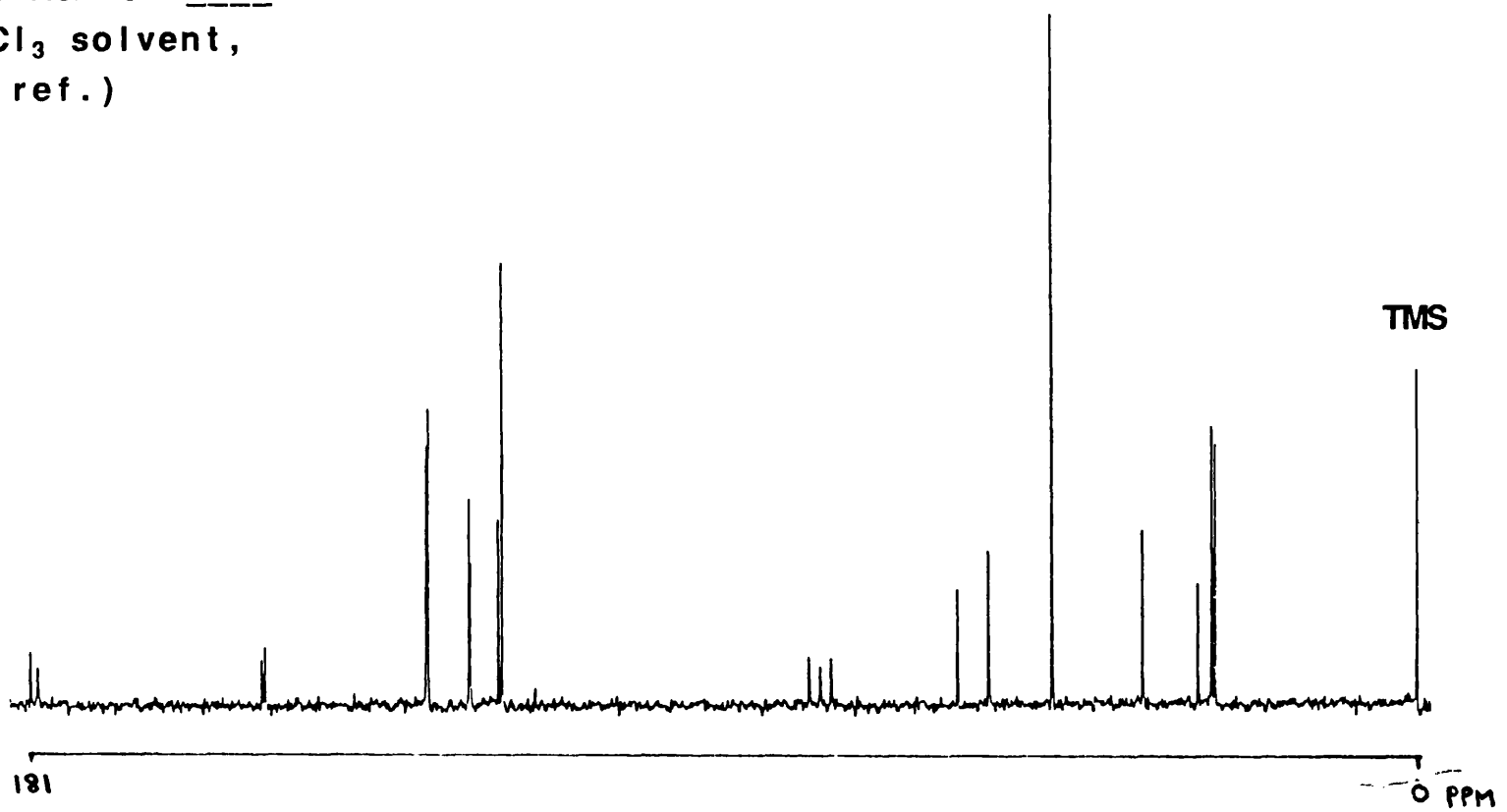
2.70 R=COEt

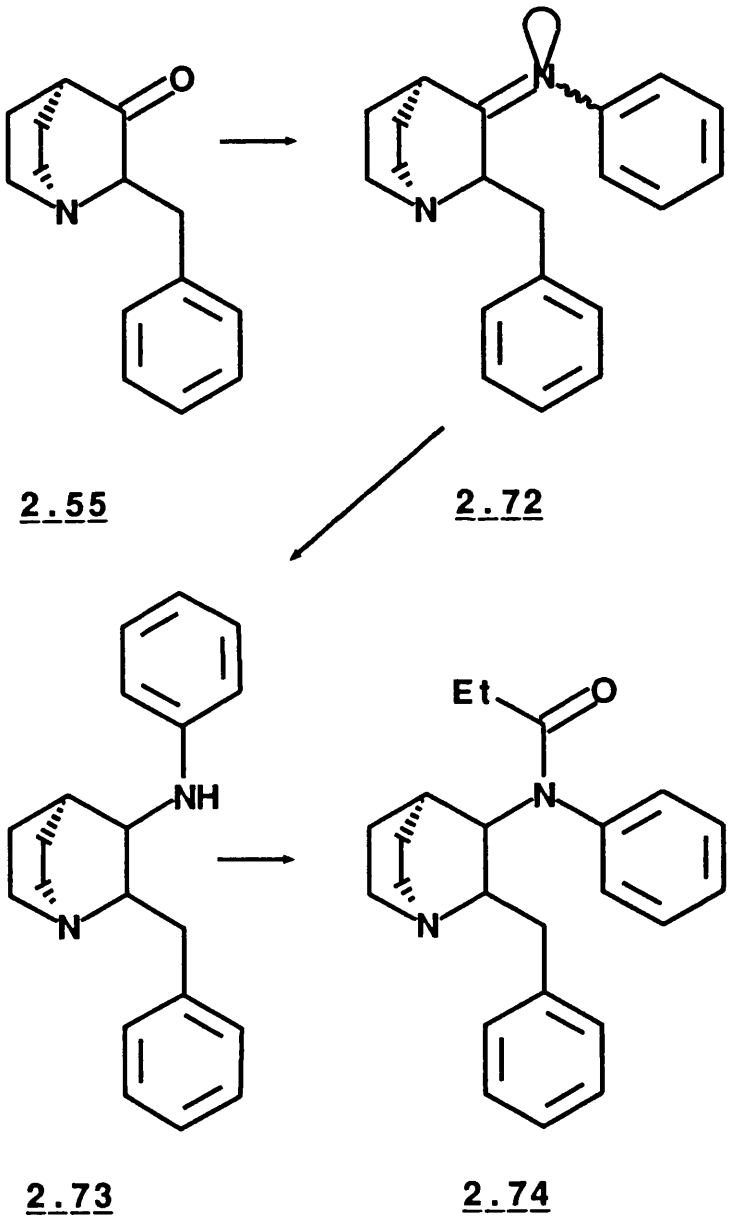
2.71 R=n-Pr

SCHEME 2.14

FIGURE 2.4

^{13} C 22.5 MHz NMR SPECTRUM OF 2.67 ($CDCl_3$ solvent, TMS ref.)

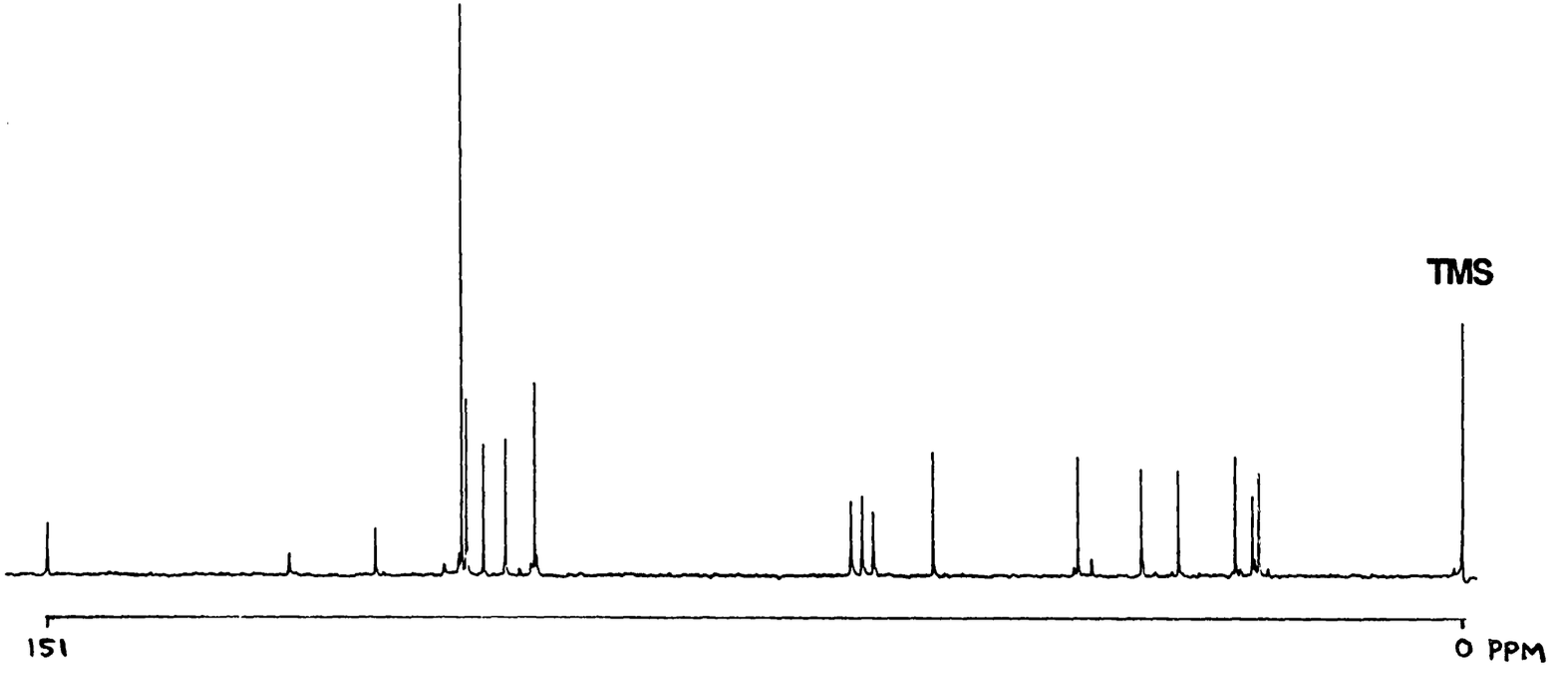


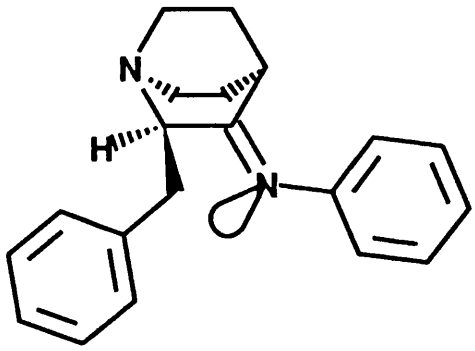


SCHEME 2.15

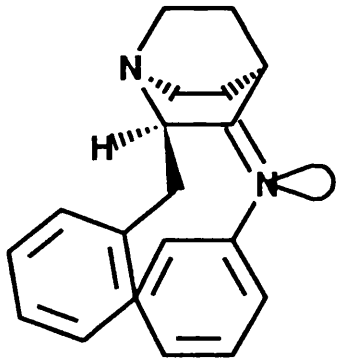
FIGURE 2.5

^{13}C 22.5 MHz NMR SPECTRUM OF 2.72 ($CDCl_3$ solvent, TMS ref.)





2.72a

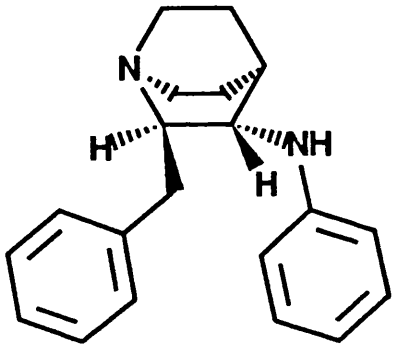


2.72b

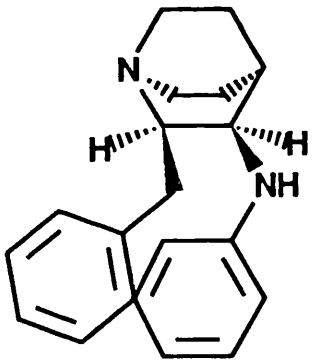
FIGURE 2.6

Reduction of 2.72 with LAH in THF gave the amine 2.73. Examination of molecular models (figure 2.7) showed the configuration with aromatic substituents cis see (2.73b) to be unfavourable due to serious interference of the aromatic rings. Further crystallisation of the mother liquors and examination of further crops of 2.73 by NMR showed no evidence for significant formation of other isomers.

Reaction of 2.73 with propionic anhydride gave the ester 2.74, the ^{13}C NMR spectrum of which is shown in figure 2.8. This indicated a single isomer as expected.



2.73a

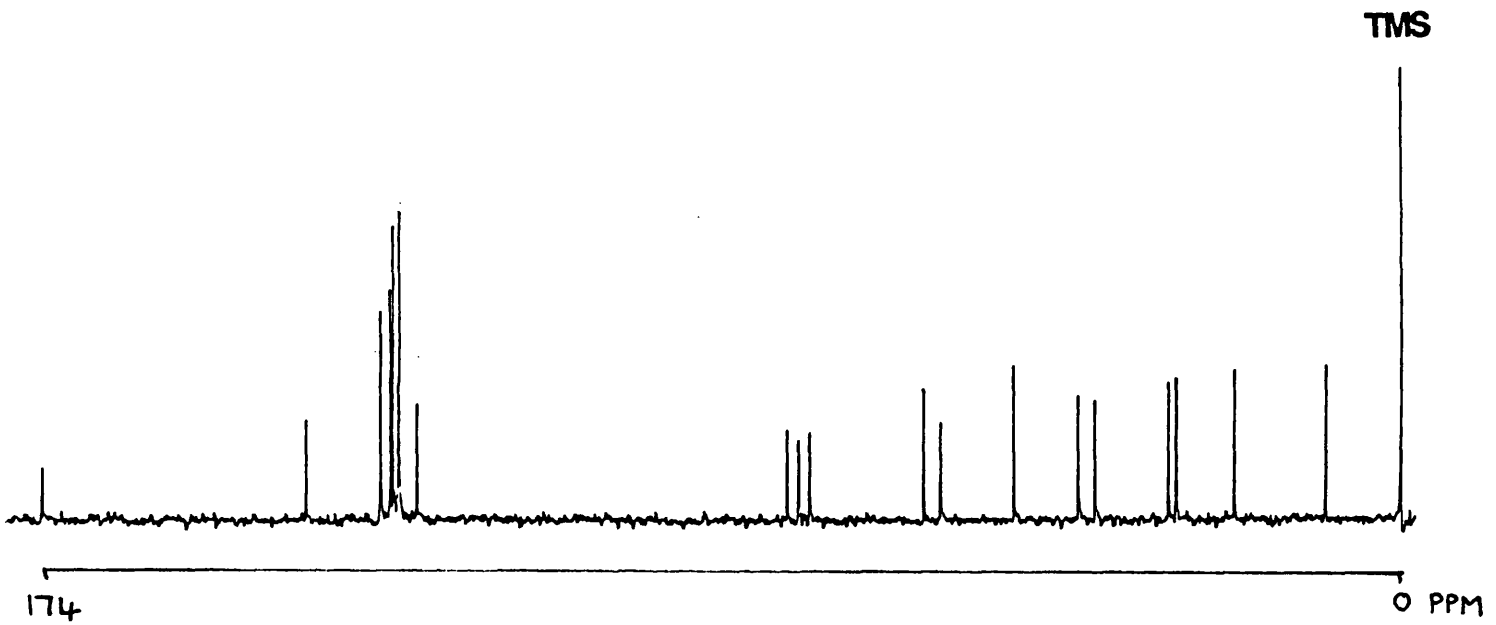


2.73b

FIGURE 2.7

FIGURE 2.8

^{13}C 22.5 MHz NMR SPECTRUM OF 2.74 ($CDCl_3$ solvent, TMS ref.)



Biological Results

The two 3-arylprodine analogues 2.62, 2.63 and the constrained N-phenethyl-3-arylprodine analogue 2.65 were inactive at up to doses of 50, 50 and 20 mg/kg respectively in the mouse hot plate test (MHP) (table 2.1). Of the fentanyl analogues, all three of the quinuclidines without the 2-benzyl moiety (2.69, 2.70 and 2.71) were also inactive at up to doses of 100, 50 and 100 mg/kg respectively. However, the constrained N-phenethyl analogue 2.74 showed a level of analgesic potency of 9.3 mg/kg which is approximately one-tenth that of both morphine and (racemic) α-prodine (2.50) (table 2.1).

This result suggests a reasonable accomodation of fit with the opioid receptors and indicates that appropriately substituted quinuclidines may be worthy of further investigation as potential analgesic agents.

TABLE 2.1

ANALGESIC ACTIVITIES ON SOME 2 , 2,3 & 2,3,3 SUBSTITUTED QUINUCLIDINES

Compound[a]	R	R_1	R_2	MHP[b]
2.62	Ph	OCOMe	H	IA[c] (50)
2.63	Ph	OCOEt	H	IA[c] (50)
2.65	Ph	OCOMe	CH_2Ph	IA[c] (20)
2.69	NPh COMe	H	H	IA[c] (100)
2.70	NPh COEt	H	H	IA[c] (50)
2.71[d]	NPh n-Pr	H	H	IA[c] (100)
2.74	NPh COEt	H	CH_2Ph	9.3(6.3-13.5)
morphine sulphate				1.2
α-prodine (α-2.50)				0.85

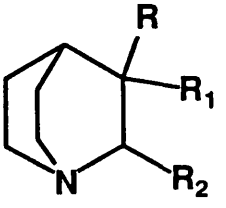
KEY FOR TABLE 2.1

a : Compounds tested as hydrochloride salts in water

b : Mouse hot plate (ED_{50} mg/kg)

c : IA=Inactive at dose level indicated

d : Tested as oxalate salt



Experimental Section

Infra-red spectra were recorded on a Unicam SP1025 spectrometer.

Melting points (uncorrected) were taken on a Gallenkamp melting point apparatus.

^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer operating at 22.5 MHz. The multiplicity of the resonances was obtained by either off-resonance (partial ^{1}H coupling) spectra, or by INEPT (Insensitive Nuclei Enhanced by Polarisation Transfer) spectra in which the phase of the signal indicated the number of protons attached to each carbon atom.

^{1}H NMR spectra were recorded using JEOL JNM-PMX 60 SI, JEOL PS100 and JEOL GX400 spectrometers. NMR samples (as bases unless stated otherwise) were prepared in 5mm o.d. tubes as approximately 10% solutions in $CDCl_3$ (unless stated otherwise) with TMS as reference.

Mass spectra were recorded on a VG 7070E mass spectrometer operating at 70 eV (EI).

Optical Rotations were measured on an Optical Activity Ltd AA-10 polarimeter.

Elemental analyses were performed by Butterworths Laboratories Ltd., Middlesex.

Formulae and abbreviations as used in the experimental section

$CDCl_3$	Deuterochloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
D_2O	Deuterium Oxide
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
HCl	Hydrochloric Acid
H_2SO_4	Sulphuric Acid
K_2CO_3	Potassium Carbonate
MeOH	Methanol
Me_2CO	Acetone
$MgSO_4$	Magnesium Sulphate (anhydrous)
NaOH	Sodium Hydroxide
Na_2SO_4	Sodium Sulphate (anhydrous)
$NaHCO_3$	Sodium Bicarbonate
Pr^iOH	Isopropanol
THF	Tetrahydrofuran
TMS	Tetramethylsilane

'Solvent was removed' - denotes evaporation under reduced pressure using a rotary evaporator.

2-Benzylidene-3-quinuclidone (2.54) [4]

A mixture of 2.44 (28g, 0.22 mol), benzaldehyde (27.5g, 0.22 mol), NaOH (0.2g) and EtOH (50 ml) were refluxed for 2 hours. Cooling and removal of the bulk of solvent gave a crude residue, which, after washing with H_2O and cold EtOH was recrystallised from EtOH to give 2.54 (34.3g, 91%) as yellow needles. m.p. 134°C, (lit [4] m.p. 130-2°C).

^1H NMR

1.8 - 2.25	δ	(m, 4H, 2 x CH_2)
2.55	δ	(t, J=2.5 Hz, 1H, 4H)
2.9 - 3.3	δ	(m, 4H, 2 x NCH_2)
7.1	δ	(s, 1H, C=CH)
7.35 - 7.65	δ	(m, 3H, 3 x Ar-H)
8.0 - 8.15	δ	(m, 2H, 2 x Ar-H)

^{13}C NMR See table 2.2

2-Benzyl-3-quinuclidone (2.55) [28]

A solution of 2.54 (10.65g, 0.05 mol) in glacial acetic acid (125 ml) was hydrogenated at atmospheric pressure and room temperature for 48 hours over Adams catalyst (0.2 g), after which time approximately 1 molar equivalent of hydrogen had been taken up. Filtration (Celite) and removal of solvent gave a crude residue, which was basified with 2N NaOH and extracted with Et_2O (3 x 50

ml). Drying (Na_2SO_4) and removal of solvent gave a colourless solid which crystallised from petroleum ether (60 - 80°) to give 2.55 (7.25g, 68%) as white granules, m.p. 76-77°C. The hydrochloride salt crystallised from EtOAc - EtOH as colourless needles. m.p. 270°C, (lit [28] m.p. 270 - 272°C).

IR ($CHCl_3$) 1725 cm^{-1} (C = O)

^1H NMR 1.8 - 2.1 δ (m, 4H, 2 x CH_2)
2.4 - 2.5 δ (m, 1H, C_4H)
2.6 - 3.0 δ (m, 7H, 2 x NCH_2, Ar CH_2 CH)
7.25 δ (s, 5H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

3-Hydroxy-3-phenylquinuclidine (2.61) [29]

To a solution of phenylmagnesium bromide in anhydrous THF [prepared from bromobenzene (12.56g, 0.08 mol) and magnesium turnings (1.92g, 0.08 mol)] was added dropwise a solution of 3-quinuclidone 2.44, (2.5g, 0.02 mol) in anhydrous THF (50 ml), and the mixture heated under reflux for 16 hours. The cooled mixture was basified with 2N K_2CO_3 (200 ml) and extracted with $CHCl_3$ (3 x 100 ml). Drying ($MgSO_4$) and removal of solvent gave crude 2.61 as a yellow oil (4.8g). Crystallisation from petroleum ether (60-80°)-Me_2CO gave 2.61 (2.3 g, 57%) as a pale crystalline solid, m.p. 170 - 172°C (lit [29] m.p. 166.8°C).

^{1}H NMR 1.4 - 2.1 δ (m, 4H, 2 x CH_2)

2.4 - 2.6 δ (m, 1H, C_4H)

3.2 - 3.9 δ (m, 7H, 3 x NCH_2, O<u>H</u>)

7.3 - 7.7 δ (m, 5H, Ar-H)

^{13}C NMR See table 2.2

3-Acetoxy-3-phenylquinuclidine (2.62)

A solution of 2.61 (0.8g, 0.004 mol) in acetic anhydride (20 ml) was heated to 80°C for 3 hours, then cooled and acidified with 2N HCl. The mixture was washed with Et_2O (3 x 100 ml; discarded) then basified with 2N NaOH and extracted with Et_2O (3 x 100 ml). Drying ($MgSO_4$) and removal of solvent gave crude 2.62 as a yellow oil (0.95g). The hydrochloride salt crystallised from Et_2O - EtOAc as a white solid (0.7g, 63%) and had m.p. 200-1°C.

^{1}H NMR 1.2 - 2.1 δ (m, 3H, 2 x CH_2)

1.9 δ (m, 3H, CH_3)

2.3 - 4.2 δ (m, 7H, 3 x NCH_2, C<u>H</u>)

7.2 - 7.6 δ (m, 5H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

3-Propionoxy-3-phenylquinuclidine (2.63)

A solution of 2.61 (1.3g, 0.0064 mol) in propionic anhydride (30 ml) was heated to 80°C for 5 hours. Work up as for 2.62 gave crude 2.63 as a yellow oil (0.95g). The hydrochloride salt crystallised from Et_2O - EtOAc as a white solid (0.55g, 29%). m.p. 118°C.

^1H NMR
1.1 δ (t, J=8Hz, 3H, CH_3)
1.2 - 1.8 δ (m, 4H, NCH_2 CH_2)
2.3 δ (q, J=8Hz, 2H, $COCH_2$)
2.4 - 3.1 δ (m, 5H, NCH_2-CH_2, C_4H)
3.5 δ (AB q, J=15Hz, 2H, NCH_2CAr)
7.1 - 7.6 δ (m, 5H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

2-Benzyl-3-hydroxy-3-phenylquinuclidine (2.64)

To a solution of phenyllithium in anhydrous Et_2O (100 ml) prepared from bromobenzene (3.8g, 0.0242 mol) and lithium (0.34g, 0.0484 mol) and left to stir at 20°C for 1 hour, was added (with cooling) a solution of 2.55 (2.6g, 0.0121 mol) in anhydrous Et_2O (100 ml). The mixture was stirred at 20°C for 3 hours then poured into a mixture of H_2O (100 ml) and Et_2O (100 ml). The aqueous layer was separated and basified with 2N Na_2CO_3, then extracted with Et_2O (3 x 100 ml). Drying ($MgSO_4$) and removal of solvent gave crude 2.64 as a yellow oil (3.3 g). Distillation in a Kugel Rohr apparatus gave 2.64 (3.0g, 85%) as a pale yellow oil which solidified on standing. b.p. 210°C @ 0.4 mmHg.

IR ($CDCl_3$) 3560 cm^{-1} (O - H)

^1H NMR 1.2 - 3.1 δ (11 aliphatic H)

3.2 δ (br s, 1H, OH exchanges with D_2O)

3.8 δ (br t, J=7.5 Hz, 1H, Ar-CH)

7.0 - 7.7 δ (m, 10H, ArH)

including 7.2 δ (s, 5H, ArH)

^{13}C NMR See table 2.2

(No C,H,N data available)

2-Benzyl-3-acetoxy-3-phenylquinuclidine (2.65)

and including the preparation of

2-Benzyl-3-phenyl-Δ 2,3-quinuclidene (2.66)

A similar method to the synthesis of 2.64 was used with a variation in the work-up procedure.

After stirring the mixture for 3 hours at 20°C, acetic anhydride (2g) was added and the mixture heated to 50°C for 2 hours, then cooled and poured into a mixture of acetic acid (100 ml) and Et_2O (100 ml). The aqueous layer was separated, basified with 2N Na_2CO_3 and extracted with Et_2O (3 x 100 ml). Drying ($MgSO_4$) and removal of solvent gave a yellow oil (3.4g). This was chromatographed on silica gel (50g) using EtOAc - $CHCl_3$ mixtures as eluant.

2.66 was obtained as an off-white solid (0.3g, 9%). The hydrochloride salt crystallised from EtOAc - Pr^iOH as a white crystalline solid m.p. 198-200°C.

EIMS M/Z 275 (M+)

IR (KCl) (Hydrochloride) 1600 cm^{-1} weak (C = C)

^1H NMR 1.3 - 3.0 δ (m, 9 aliphatic H)
3.55 δ (s, 2H, CH_2Ph)
7.15 δ (s, 5H, ArH)
7.20 δ (s, 5H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

A further 1.6g of combined column fractions were converted to the oxalate salt. This crystallised from Me_2CO (slowly over several days) as colourless needles. Liberation of the free base gave 2.65 (0.8g, 21%) as a colourless oil. The hydrochloride salt crystallised from EtOAc - Me_2CO as a white solid m.p. 175-7°C.

^1H NMR 1.2 - 1.8 δ (m, 5 aliphatic H)
2.0 δ (s, 3H, $COCH_3$)
2.5 - 3.5 δ (m, 7 aliphatic H)
7.1 - 7.7 δ (m, 10H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

3-Phenyliminoquinuclidine (2.67)

A mixture of 2.44 (9g, 0.072 mol), zinc chloride (1g) and toluene (200 ml) were azeotropically distilled in a Dean-Stark apparatus for 16 hours. The cooled mixture was filtered and distilled under reduced pressure to give 2.67 (11.05g, 77%) as a colourless oil, b.p. 125° @ 0.2 mmHg .

^{1}H NMR 1.6 - 2.2 δ (m, 4H, 2 x NCH_2CH_2)

2.7 - 3.2 δ (m, 5H, 2 x NCH_2, C4H)

3.4 δ (s, 1H, NCHC=N)

3.6 δ (s, 1H, NCHC=N)

6.7 - 6.9 δ (m, 2H, ArH)

7.0 - 7.5 δ (m, 3H, ArH)

^{13}C NMR See table 2.2

3-Phenylaminoquinuclidine (2.68)

To a stirred mixture of LAH (8g, 0.21 mol) in anhydrous THF (100 ml) was added, dropwise, a solution of 2.67 (11g, 0.055 mol) in anhydrous THF (100 ml). The mixture was refluxed for 1 hour then cooled in an ice bath. After cautious dropwise addition of 2N NaOH (15 ml) and 1 hour stirring at 10°C, the slurry was filtered

and the cake washed with CH_2Cl_2 (200 ml). Drying ($MgSO_4$) and removal of solvent gave a yellow solid which crystallised from cyclohexane to give 2.68 (5.96g, 54%) as a white solid, m.p. 112°C.

^{1}H NMR 1.2 - 2.1 δ (m, 5H, 2 x CH_2, CH)
2.3 - 3.1 δ (m, 4H, 2 x CH_2N)
3.2 - 3.6 δ (m, 2H, CH_2N)
3.8 δ (br s, 1H, NH, exchanges with D_2O)
6.4 - 6.8 δ (m, 3H, ArH)
7.0 - 7.3 δ (t, J=7.5Hz, 2H, ArH)

^{13}C NMR See table 2.2

3-(N-acetylanilino)quinuclidine (2.69)

A solution of 2.68 (2g, 0.01 mol) in acetic anhydride (15 ml) was heated to 80°C for 1 hour. Work up as for 2.62 gave crude 2.69 as a yellow oil (2.3g). The hydrochloride salt crystallised from EtOAc-Me_2CO as a pale solid (1.1g, 40%), m.p. 192-3°C.

^{1}H NMR 0.9 - 3.9 δ (m, 14 aliphatic H)
including 1.8 δ (s, 3H, $COCH_3$)
4.7 δ (br t, J=8.5Hz, 1H, C3H)
7.15 - 7.6 δ (m, 5H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

3-(N-propionylanilino)quinuclidine (2.70)

A solution of 2.68 (2g, 0.01 mol) in propionic anhydride (15 ml) was heated to 80°C for 3 hours. Work up as for 2.62 gave crude 2.70 as a yellow oil (2.7g). The hydrochloride salt crystallised from EtOAc-EtOH as a white solid (0.6g, 20%), m.p. 183-4°C.

^{1}H NMR
1.0 δ (t, 3H, CH_3)
1.5 - 2.3 δ (m, 6 aliphatic H)
2.5 - 3.0 δ (m, 6 aliphatic H)
3.4 δ (br t, J=7.5 Hz, 1H, C4H)
4.7 δ (br t, J=7.5 Hz, 1H, C3H)
7.1 - 7.6 δ (m, 5H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

3-(N-propylanilino)quinuclidine (2.71)

To a stirred mixture of LAH (0.75g, 0.02 mol) in anhydrous THF (25 ml), was added dropwise a solution of 2.70 (1.3g, 0.005 mol) in anhydrous THF (25 ml). The mixture was heated under reflux for 16 hours then cooled in an ice bath. Work up as for 2.68 gave a pale solid (1.0g). Recrystallisation from Me_2CO gave 2.71, (0.70g, 57%) as white crystals, m.p. 217-219°C. The hydrochloride salt was found to be hygroscopic and could not be obtained pure. The oxalate salt crystallised from EtOH as a white solid, m.p. 162-3°C.

1½ moles of oxalic acid per mole of base from analytical results (table 2.3).

EIMS M/Z 244 (M+)

^{1}H NMR 0.6 - 2.1 δ (m, 9 aliphatic H)

including 0.8 δ (t, J=7.5Hz, 3H, CH_3)

2.5 - 3.6 δ (m, 10 aliphatic H)

6.9 - 7.5 δ (m, 5H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

2-Benzyl-3-phenyliminoquinuclidine (2.72)

A mixture of 2.55 (5.2g, 0.0242 mol), freshly distilled aniline (11g, 0.121 mol), zinc chloride (0.75g) and toluene (150 ml) were azeotropically distilled in a Dean-Stark apparatus for 6 days. The cooled mixture was filtered and distilled under reduced pressure to give crude 2.27 as a red oil (6.1g). This was crystallised, first from petroleum ether (60 - 80°) then petroleum ether (30 - 40°), to give 2.72 (2.2g, 31%) as pale yellow crystals, m.p. 72-3°C.

^{1}H NMR 1.6 - 2.1 δ (m, 4H, 2 x CH_2)

2.6 - 4.0 δ (m, 8 aliphatic H)

6.8 - 7.6 δ (m, 10H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

2-Benzyl-3-phenylanilinoquinuclidine (2.73)

To a stirred mixture of LAH (1.89g, 0.05 mol) in anhydrous THF (30 ml) was added, dropwise, a solution of 2.72 (3.6g, 0.0124 mol) in anhydrous THF (30 ml). The mixture was heated under reflux for 1 hour, then worked up as for 2.68 to give 2.73, (2.5g, 69%) as pink crystals, m.p. 122-3°C.

^{1}H NMR 1.4 - 2.2 δ (m, 6 aliphatic H)

2.5 - 3.4 δ (m, 8 aliphatic H)

including 3.3 δ (br s, NH, exchanges with D_2O)

7.4 δ (s, 5H, ArH)

^{13}C NMR See table 2.2

Analysis See table 2.3

2-Benzyl-3-(N-propionylanilino)quinuclidine (2.74)

A solution of 2.73 (2.3g, 0.008 mol) in propionic anhydride (25 ml) was heated to 80°C for 3 hours. Work up as for 2.62 gave crude 2.74 as a yellow oil (2.5g). Crystallisation from petroleum ether (40 - 60°) gave 2.74, (1.8g, 66%) as yellow crystals m.p. 82-4°C. The hydrochloride salt crystallised from benzene-Me_2CO as white granules, m.p. 208-9°C.

^1H NMR 0.9 - 1.4 δ (m, 5 aliphatic H)

including 1.0 δ (t, J=7.5Hz, 3H, CH_3)

1.5 - 2.5 δ (m, 5 aliphatic H)

2.6 - 3.5 δ (m, 7 aliphatic H)

4.8 δ (m, 1H, CHNAr)

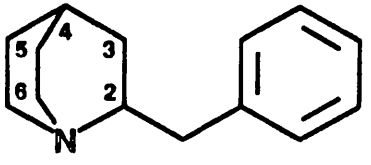
^{13}C NMR See table 2.2

Analysis See table 2.3

TABLE 2.2 ^{13}C NMR DATA ON SOME 2 , 2,3 & 2,3,3 SUBSTITUTED QUINUCLIDINES

Compound[a]	C_2	C_3	C_4	C_5	C_6	Benzyl	ArCO	COR	Aromatics
2.44	62.9	204.2	39.7	25.8	47.0	——	——	——	——
2.45	130	205.3	40.4	28.2	47.6	——	——	——	124.6-144.0
2.55	72.4	207.5	49.8	26.1,27.6	34.5,41.0	41.9	——	——	127.2-140.0
2.61	60.8	72.5	32.9	20.2,21.4	33.5,41.2	——	——	——	127.0-144.6
2.62	59.7	82.3	31.6	22.8	46.3,47.3	——	169.7	21.8	125.8-142.6
2.63	59.9	82.1	31.6	22.9	46.4,47.4	——	173.0	21.9,28.4	125.8-142.6
2.64	64.3	75.2	35.8	21.9,23.3	33.4,41.1	48.9	——	——	125.8-146.4
2.65	68.9	84.0	33.2	23.0,23.6	28.0,41.1	48.7	169.6	21.7	125.8-142.0
2.66	126	128	34.3	29.5	37.5	49.3	——	——	126.0-146.4
2.67	55.5,59.5	179.8,180.8	28.3,35.5	26.1,26.5	47.2	——	——	——	119.1-150.6
2.68	57.2	50.3	25.2	20.1,26.1	46.9,47.5	——	——	——	113.2-147.5
2.69	53.6	53.4	25.9	20.8,28.9	46.5,47.7	——	171.3	23.6	128.5-141.1
2.70	53.8	53.6	25.9	20.8,28.9	46.6,47.6	——	174.4	9.5,28.5	128.4-140.6
2.71	55.1	54.3	24.3	20.5,24.3	47.0,47.7	——	——	11.6,19.7,26.8	121.5-150.6
2.72	67.9	182.2	29.0	26.0,26.8	36.5,41.1	49.3	——	——	119.5-151.1
2.73	67.1	58.0	26.2	19.8,26.0	39.8,41.4	49.9	——	——	113.4-147.6
2.74	61.2	58.9	29.7	21.3,28.8	39.2,41.3	49.6	174.3	9.6,28.7	126.0-140.3

a : Free base in $CDCl_3$ with TMS as reference



Analytical Data Table 2.3

Compound	Formula		C	H	N
2.55	$C_{14}H_{17}NO$	Calc	78.10	7.96	6.51
		Found	77.65	7.95	6.62
2.62	$C_{15}H_{19}NO_2.HCl$	Calc	63.94	7.15	4.97
		Found	63.43	7.16	4.91
2.63	$C_{16}H_{21}NO_2HCl.H_2O$	Calc	61.24	7.71	4.46
		Found	61.47	7.81	4.32
2.65	$C_{22}H_{25}NO_2.HCl$	Calc	71.05	7.05	3.77
		Found	70.88	7.08	3.67
2.66	$C_{20}H_{21}N.HCl$	Calc	77.03	7.11	4.49
		Found	76.87	7.21	4.51
2.69	$C_{15}H_{20}N_2O.HCl\frac{1}{2}H_2O$	Calc	63.25	7.96	9.22
		Found	63.12	7.44	9.18
2.71	$C_{16}H_{24}N_2.\frac{3}{2}(C_2H_2O_4)$	Calc	60.14	7.17	7.38
		Found	60.58	7.26	7.46
2.72	$C_{20}H_{22}N_2$	Calc	82.72	7.64	9.65
		Found	82.32	7.71	9.79
2.73	$C_{20}H_{22}N_2$	Calc	82.15	8.27	9.58
		Found	82.44	8.39	9.54
2.74	$C_{23}H_{28}N_2O$	Calc	79.27	8.10	8.04
		Found	79.03	8.16	8.13

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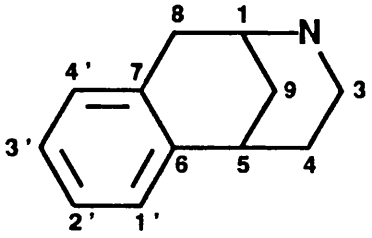
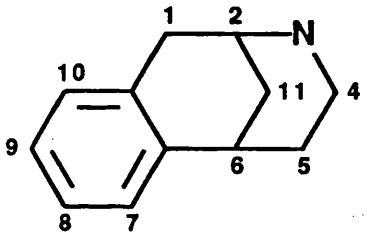
BENZOMORPHAN INTRODUCTION

The 6,7-benzomorphan class of compounds (described in Chemical Abstracts as the 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines) are an extensively investigated and important class of synthetic narcotic analgesics.[1,2] The parent ring system of the original (benzomorphan) and Chemical Abstracts numbering systems are shown in 3.1 and 3.2 respectively.



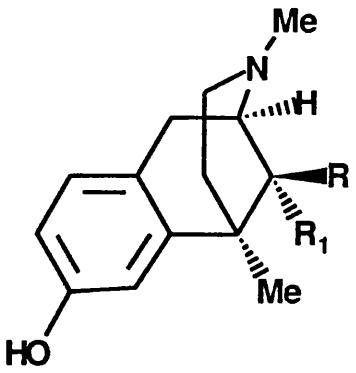
3.1



3.2

In this chapter, the original nomenclature has been used throughout.

Metazocine 3.3 is usually regarded as the parent 6,7-benzomorphan. The 5,9 methyl groups can be oriented either cis as 3.3a, or trans as 3.3b. These isomers are designated the α and β isomers respectively.



3.3a R=H R_1=Me

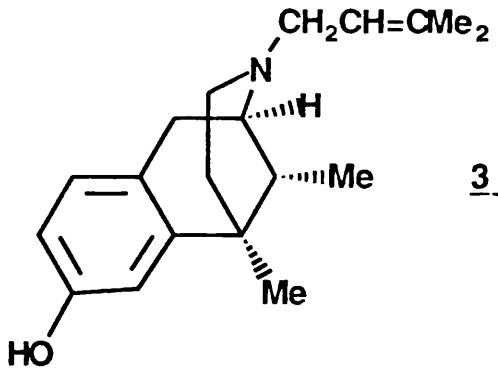
3.3b R=Me R_1=H

A marked difference in biological activity exists between these 2 isomers, with the β isomer approximately 10 times more active in rodent tests.[1]

Due to the chirality of positions 1 and 5, an antipodal pair exists for each (α or β) benzomorphan.

When the antipodal pairs are resolved, the vast majority of the analgesic activity is found to reside in the laevo benzomorphan, which is configurationally related to (-) morphine. The dextro enantiomers of 3.3a/b are analgesically inactive and generally more toxic than their laevo counterparts.

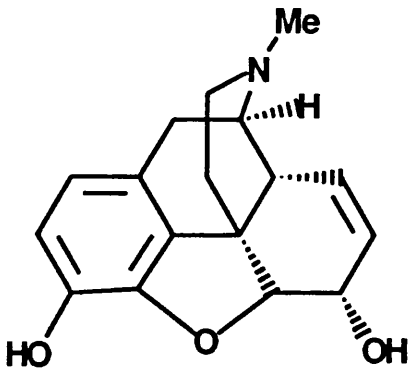
One of the best known of the 6,7-benzomorphans is pentazocine 3.4, which is firmly established as a clinically important analgesic.[3]



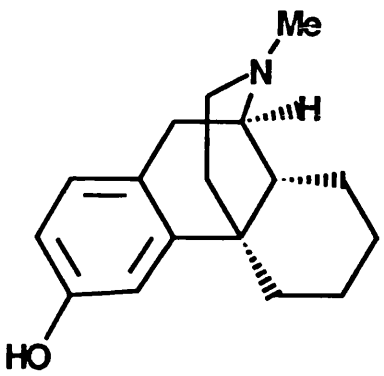
3.4

The 6,7-benzomorphans were originally synthesised in the early 1950s, during attempts to rationalise the structure of morphine 3.5 and in doing so separate its analgesic properties from undesired side effects (respiratory depression, physical dependence

liability (PDC), etc.) This approach was furthered by the discovery that the morphinan levorphanol 3.6, obtained by removal of functional groups from morphine, was 3 to 4 times more potent, whilst showing a similar level of side effects.[4]



3.5

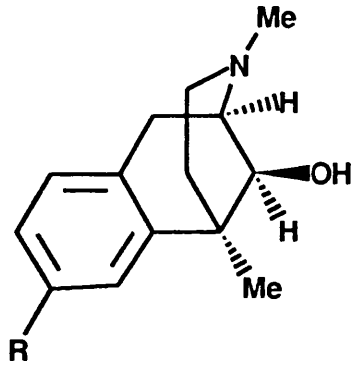


3.6

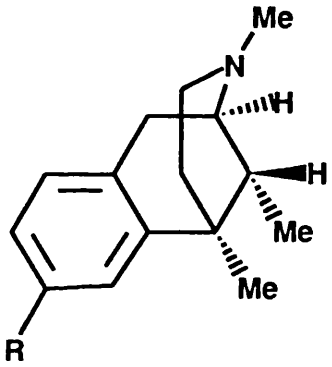
Extrapolation of these results by further rationalisation of the morphinoid structure, for example as in the 6,7-benzomorphans, might therefore seem a promising strategy.

Since these early experiments, a large number of 6,7-benzomorphans have been synthesised and their pharmacology investigated. In general, the structure-activity profiles of the 6,7-benzomorphans parallel those seen in the morphine and morphinan series. For instance, introduction of a phenolic OH at position 2' increases activity, whilst masking the oxygen function as, for example, the methyl ether reduces it (c.f. morphine and codeine). Acetylation at 2' generally increases activity compared to the parent phenolic derivative (c.f. morphine and heroin).

However, there are exceptions and activity may often be highly dependent on the overall substitution pattern. For instance, in 3.7 introduction of OH at 2' did not increase activity in rodent tests although O-methylation did reduce it. This is in contrast to 3.8 which showed the expected pattern of activity, i.e. OAc at 2' having greatest activity and OMe the least (table 3.1).[1,5]



3.7



3.8

R	ED_{50}
H	63.8
OH	79.9
OMe	>100

R	ED_{50}
H	27.3
OH	3.0
OMe	9.8
OAc	1.2
morphine sulphate	1.2

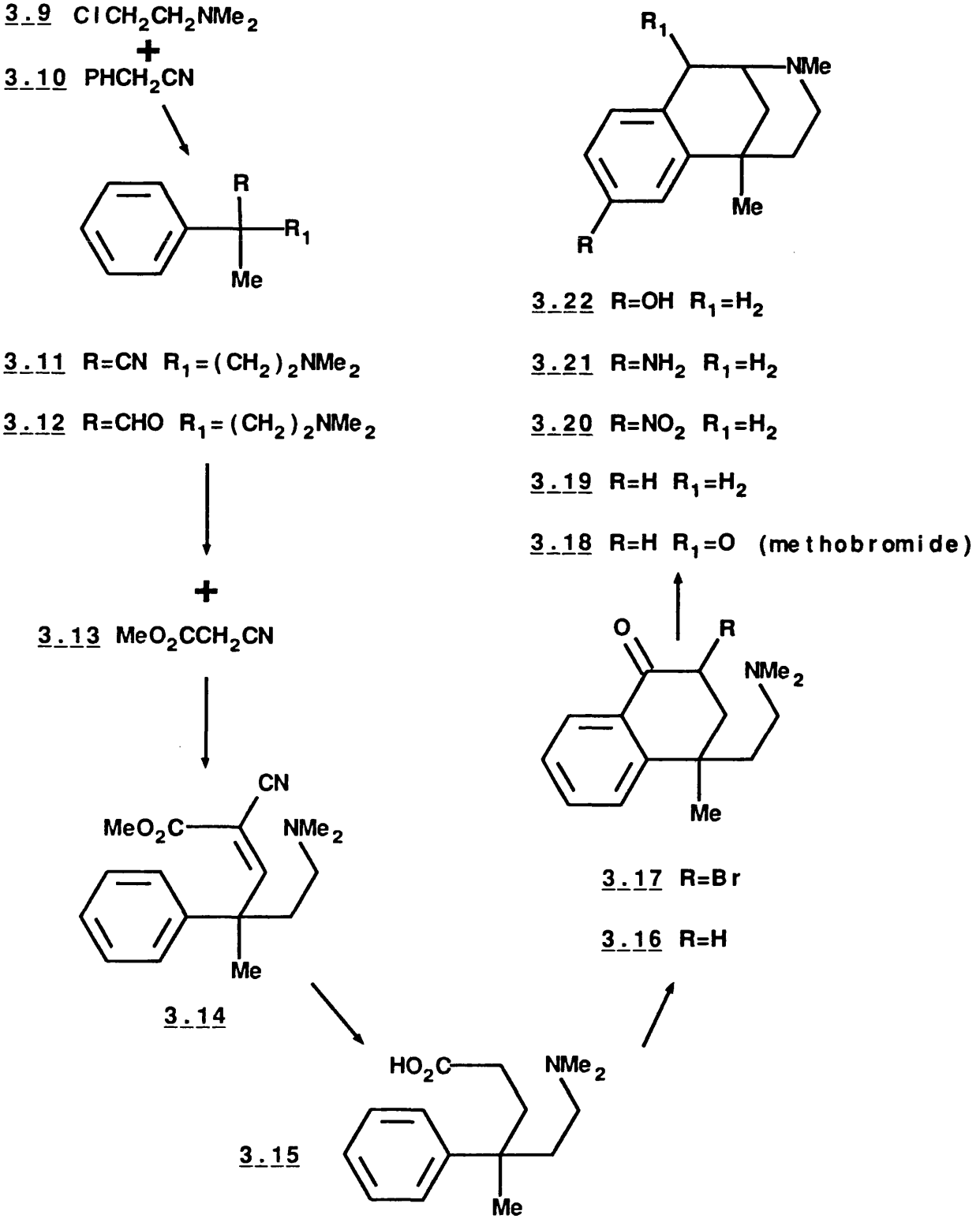
TABLE 3.1 [1] (ED_{50} mg/kg MHP)

ANALGESIC ACTIVITIES OF SOME 9-HYDROXY-5-METHYL & 5,9-DIMETHYL -6,7-BENZOMORPHANS

Chemistry

One of the original synthetic methods used for the preparation of the 6,7-benzomorphans is illustrated in scheme 3.1.[6]

Alkylation of methylbenzyl cyanide 3.10 with 1-chloro-2-dimethylaminoethane 3.9 in the presence of base gave 3.11, which was selectively reduced to the aldehyde 3.12. Condensation of 3.12 with methyl cyanoacetate 3.13 gave 3.14 which was hydrogenated over Adams catalyst . Subsequent hydrolysis and decarboxylation gave amino acid 3.15. Intramolecular ring closure, bromination and further cyclisation led to the methobromide of 3.18. Elimination of methyl bromide, followed by Wolf-Kishner reduction gave 5-methyl-6,7-benzomorphan 3.19 in 5% overall yield. A phenolic OH could subsequently be introduced at the 2' position by nitration and diazotization with aqueous work up.


3.9 ClCH2CH2NMe2
+
3.10 PHCH2CN
R
R1
Me
3.11 R=CN R1=(CH2)2NMe2
3.12 R=CHO R1=(CH2)2NMe2
+
3.13 MeO2CCH2CN
CN
MeO2C
NMe2
Me
3.14
HO2C
NMe2
Me
3.15
R1
NMe
Me
R
3.22 R=OH R1=H2
3.21 R=NH2 R1=H2
3.20 R=NO2 R1=H2
3.19 R=H R1=H2
3.18 R=H R1=O (methobromide)
O
R
NMe2
Me
3.17 R=Br
3.16 R=H

SCHEME 3.1 [6]

A later method which has found wide use in the synthesis of 6,7-benzomorphans is the Grewe[7] synthesis. This was originally used for the synthesis of morphinan derivatives and has since been successfully adapted for use with 6,7-benzomorphans. The Grewe method is illustrated for the synthesis of 3.27 in scheme 3.2[8]. Reaction of 1,3,4-trimethylpyridinium iodide 3.23 with p-methoxybenzylmagnesium chloride gave 3.24. The enamine double bond was reduced with sodium borohydride to give 3.25 which cyclised under acid conditions to give the 2,5,9-trimethyl-2'-methoxy-6,7-benzomorphan 3.26. O-Demethylation with HBr gave the 2'-hydroxy derivative 3.27. The overall yield was approximately 25%.

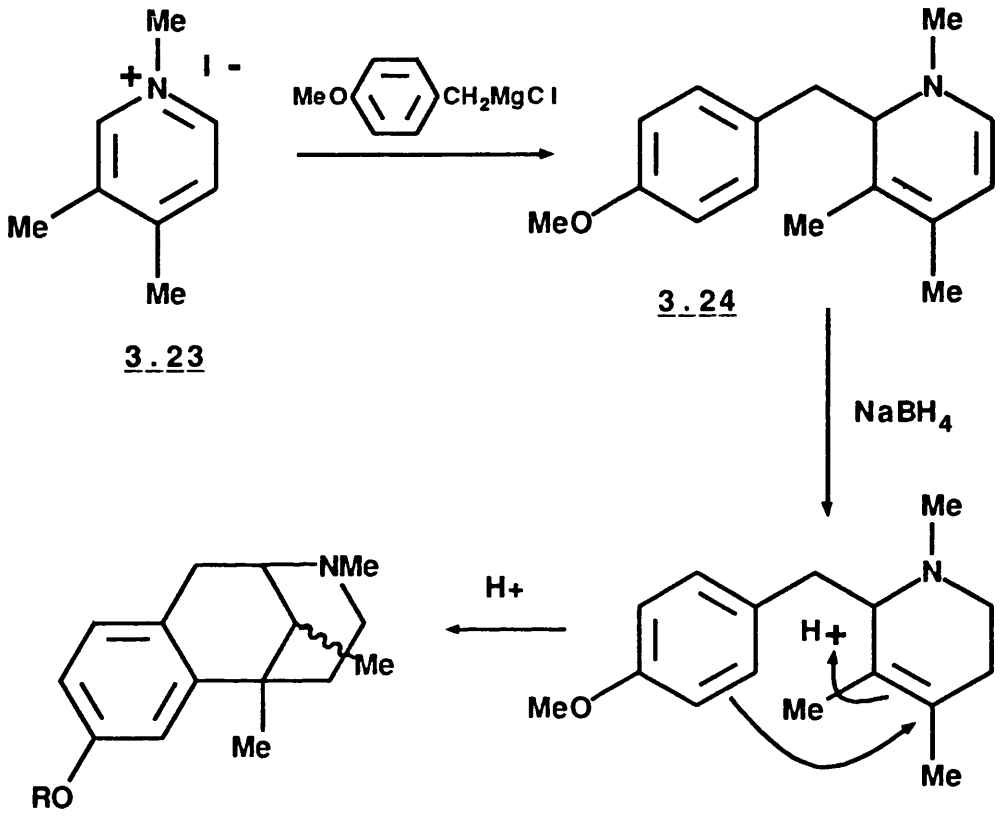
One major advantage of the Grewe method is the ability to alter the alkyl substitution pattern of the final product by choice of suitably substituted pyridine starting material.

Structure-Activity Relationships

As in the morphine and morphinan series, variation of substituents on the aromatic ring, on nitrogen and elsewhere in the 6,7-benzomorphan system may have a profound effect on the type and magnitude of biological activity. The most frequently found structure variations used to bring about these changes are at the 2', 2, 5 and 9 positions.

2' Substituents

As mentioned previously, changes here generally mirror those seen



3.23

3.24

3.25

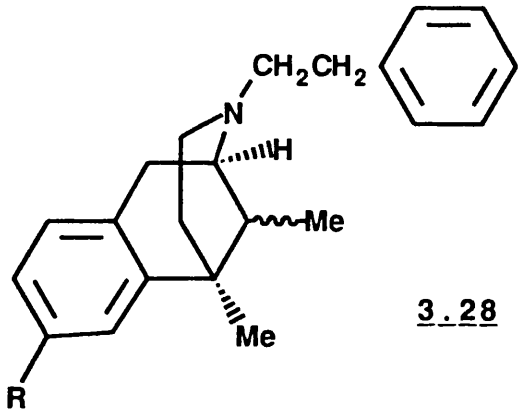
3.26 R=Me

3.27 R=H

SCHEME 3.2 [8]

in the morphinan series. A change from H to OH usually effects an increase in activity which is further increased by acetylation. Conversely, analgesic activity is decreased when the phenolic OH is masked (usually by methylation).

Structure 3.28 and the analgesic activity of some derivatives are shown as examples in table 3.2



3.28

R	ED_{50}
OAc	0.19
OH	0.25
OMe	6.5
OCH_2OMe	3.3
$OCOArNO_2$	0.41
morphine sulphate	1.2

TABLE 3.2 [1] (ED_{50} mg/kg MHP)

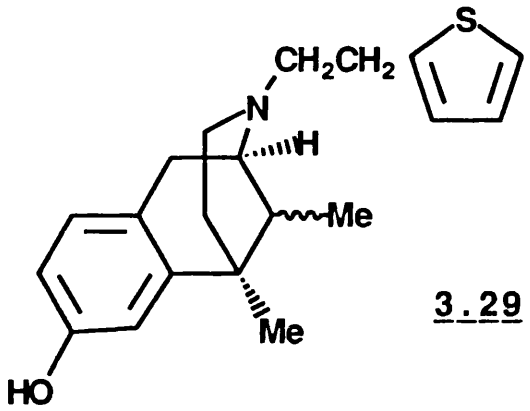
ANALGESIC ACTIVITIES OF SOME

5,9-DIMETHYL-2-PHENETHYL

6,7-BENZOMORPHANS

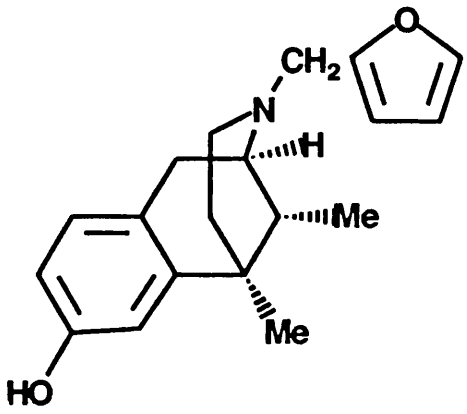
2-Substituents

The effect of substitution at nitrogen again parallels that seen in the morphine/morphinan series. Alkyl groups other than methyl tend to have reduced agonist activity (i.e. ethyl > propyl > butyl) whereas n-pentyl is approximately equipotent. Several aralkyl groups confer increased agonist activity on the system; the most commonly used is the phenethyl group. Others which have been found to be effective are p-aminophenethyl, thienylethyl and 2-tetrahydrofurfuryl. The N-thienylethyl derivative, 3.29, is amongst the most potent benzomorphans, with activity approximately 40 times morphine.[10]

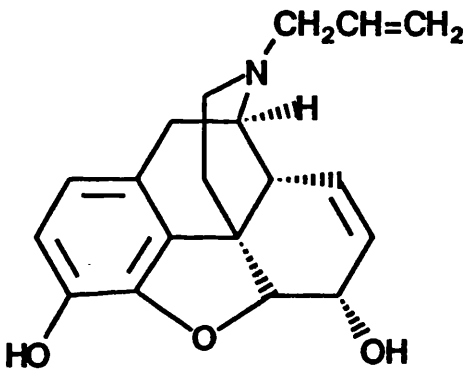


3.29

Substitution of N-methyl by allyl, cyclopropylmethyl (CPM) and certain others, for example furylmethyl, generally confer antagonist properties on the benzomorphan system. For example, the N-furylmethyl benzomorphan 3.30[10] is approximately equipotent as an antagonist to N-allyl morphine (nalorphine), 3.31.



3.30

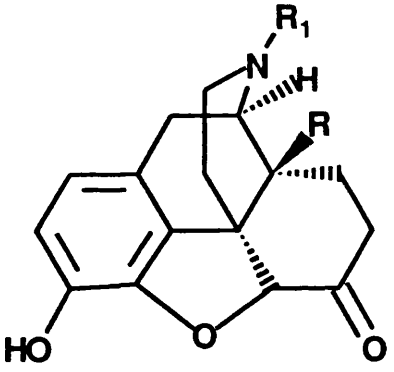


3.31

Other Substituents

9-Substituents

The introduction of a hydroxyl group at position 14 in morphinoid compounds generally increases agonist activity. Thus, 14-hydroxydihydromorphinone 3.32 is found to be between 2 and 4 times more potent than dihydromorphinone 3.32a.[1]



3.32 R=OH R_1=Me

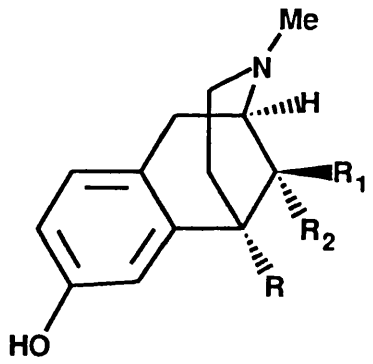
3.32a R=H R_1=Me

3.33 R=OH R_1=allyl

3.33a R=OH R_1=CPM

Several therapeutically well known narcotic antagonists are 14-hydroxy substituted e.g. naloxone 3.33 and naltrexone 3.33a.

Introduction of a hydroxyl group at the corresponding position 9 in the 6,7-benzomorphans usually results in a reduction in analgesic activity. Examples are shown in the derivatives 3.34-3.39.



3.34 R=Et R_1=H R_2=OH

3.35 R=Et R_1=OH R_2=H

3.36 R=Et R_1=H R_2=H

3.37 R=Me R_1=H R_2=OH

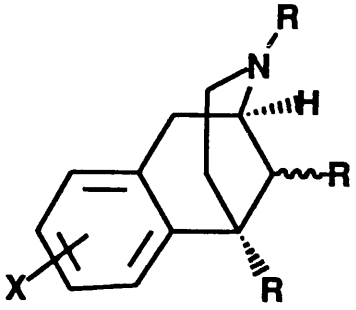
3.38 R=Me R_1=OH R_2=H

3.39 R=Me R_1=H R_2=H

When R was ethyl, activity was reduced by the introduction of a 9-hydroxyl β (trans) as in 3.34, and abolished altogether when the 9-hydroxyl was oriented towards the nitrogen (α form, 3.35). This pattern was reversed when R was methyl, as in 3.39. The 9α-hydroxy derivative 3.38 was approximately one-eighth as active as 3.39, whereas the 9β-hydroxy derivative 3.37 was inactive.[5,11]

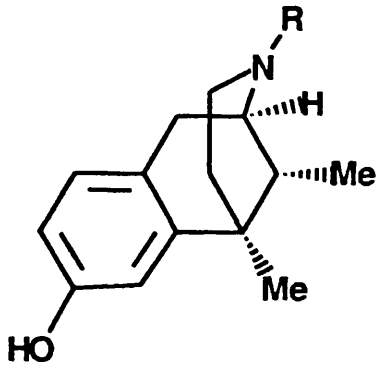
BENZOMORPHAN DISCUSSION

Derivatives of the 6,7-benzomorphans 3.40 constitute a class of compounds with opiate-like analgesic activity.[1,2]



3.40

The class includes examples of both agonists, e.g. 3.41, 3.42 and antagonists e.g. 3.43.



3.41 R=Me

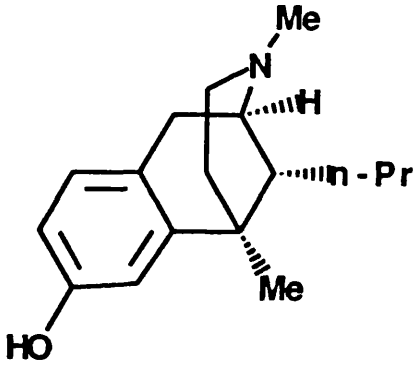
3.42 R=CH_2CH_2Ph

3.43 R=allyl

Over the past few decades, a large number of 6,7-benzomorphans have been synthesised, not only in an effort to produce a potent analgesic with the minimum of undesired properties, but also as a means of studying the nature of opioid receptors. One approach to

this problem in the benzomorphan series has been the optical resolution of enantiomeric isomers.[12] It has been shown that the laevo forms of the benzomorphans are configurationally related to morphine and are predominantly responsible for the analgesic properties of the racemate. Additionally, several (-) benzomorphans have been shown to lack a physical dependence capacity (PDC) in rhesus monkeys.[12-14]

In the late 1970s the optical resolution of (±) -2,5-dimethyl-2'-hydroxy-9α and 9β-propyl-6,7-benzomorphan 3.44

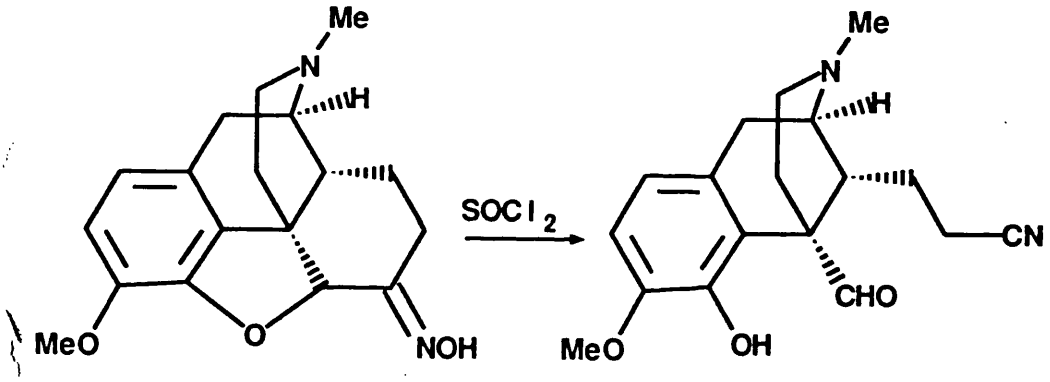


3.44

was achieved and amongst others, the (-)-9β isomer was shown to warrant further investigation as a potent analgesic with little or no PDC.[15] However, due to the relatively complex and low yielding method (necessarily involving fractional crystallation of diastereomeric salts) we were led to investigate an alternate stereospecific route to these compounds.

Historical Background

In the 1920s, during the course of a structure determination of morphine using chemical degradation to known products, Schopf[16] subjected dihydrocodeinone oxime, 3.45, to Beckmann rearrangement and isolated (-)-9α-(2-cyanoethyl)-5α-formyl-1'-hydroxy-2'-methoxy-6,7-benzomorphan 3.46 as the major product (scheme 3.3).

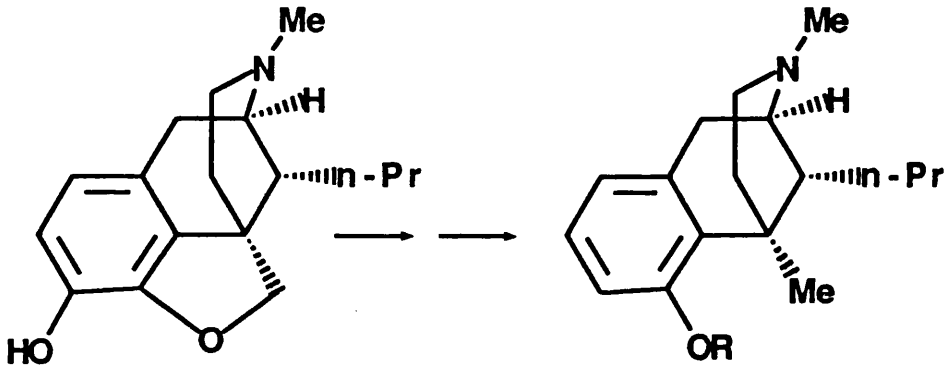


3.45 3.46

SCHEME 3.3 [16]

Appropriate substituents of this type in the 5 and 9 positions of 3.46 offered the possibility of preparing a series of optically pure (-)-5,9-dialkylbenzomorphans similar in nature to 3.44, in reasonable yield without the need for optical resolution.

The conversion of 3.46 to a 5,9-dialkyl derivative similar to 3.44 requires the reduction of the 5 and 9 substituents and deoxygenation at position 1', together with O-demethylation of the 2'-methoxy substituent. During the course of these transformations in this laboratory, cyclisation occurred to give a series of 5α, 1'-methyleneoxybenzomorphans exemplified by the 2'-hydroxy derivative, 3.54. The new methyleneoxy ring was subsequently opened to give the 1'-hydroxy and 1'-methoxy-6,7-benzomorphans, 3.60 and 3.61 respectively (see later schemes).

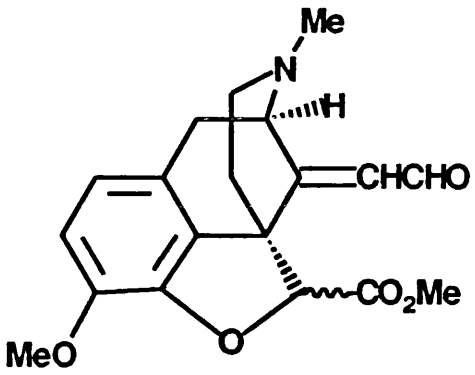


3.54

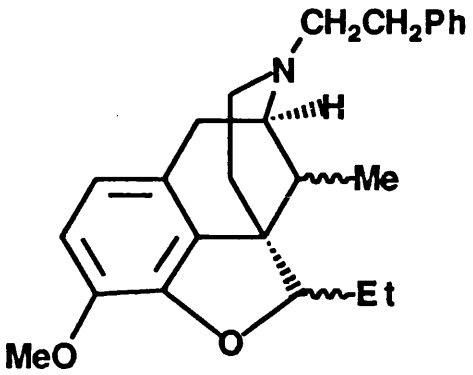
3.60 R=H

3.61 R=Me

Other workers have previously synthesised 5α,1'-methyleneoxy-6,7-benzomorphan derivatives. In 1967, workers investigating the ozonolysis of thebaine isolated low yields of 3.47, but no biological data were presented.[17]

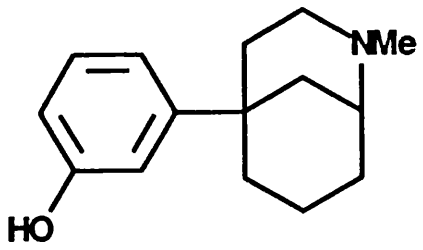


3.47

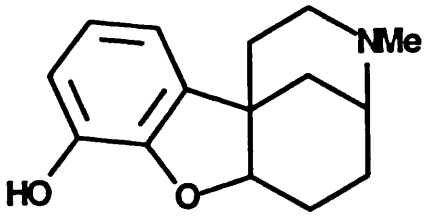


3.48

In 1963, a group[18] converted codeine via N-phenethyl-7,8-dihydroxydihydro desoxycodeine into the 5α,1'methyleneoxy benzomorphan 3.48 which had twice the potency of morphine in the mouse hot plate test. Additionally, an oxide bridged 5-(m-hydroxyphenyl)morphan 3.49a was recently reported[19], but lacked in vivo analgesic activity in contrast to the parent



3.49



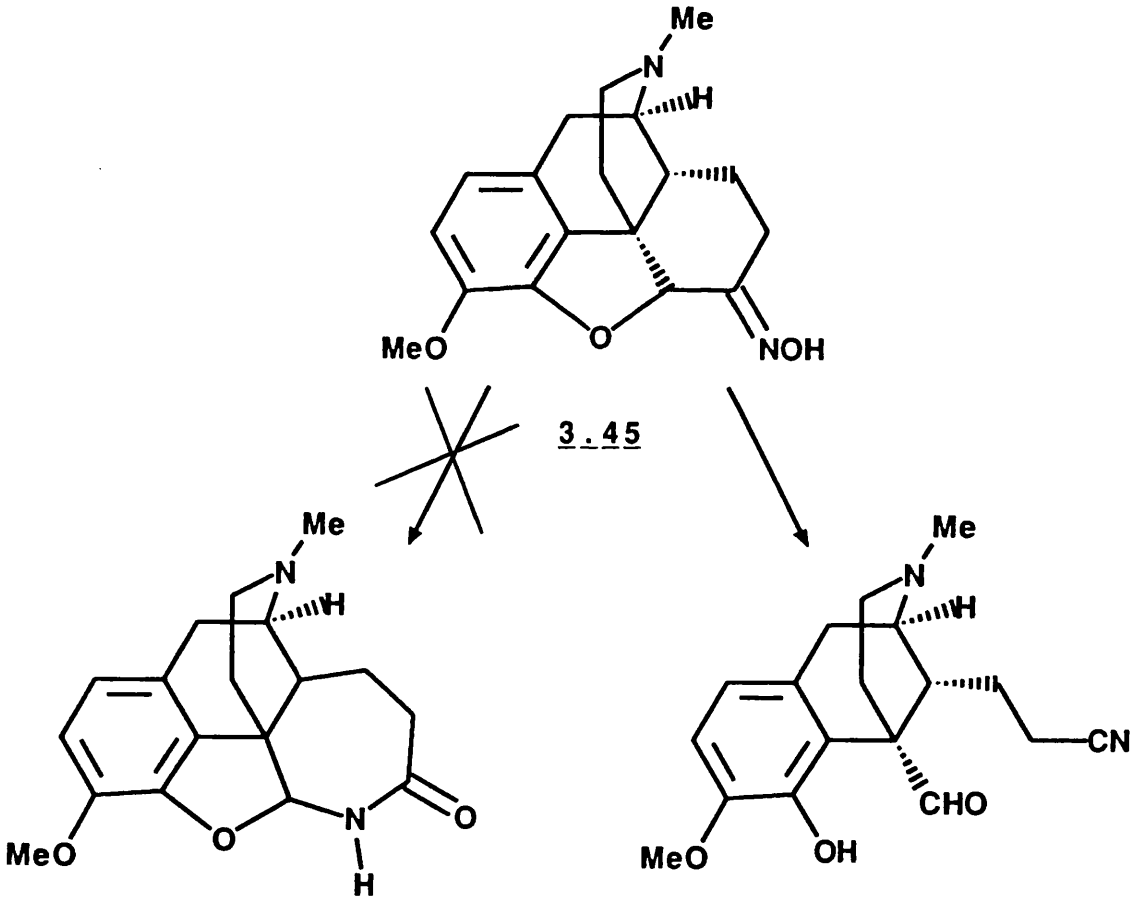
3.49a

5-(m-hydroxyphenyl)morphan 3.49. The constrained stereochemistry of the phenyl ring in 3.49a was presumed to be unsuitable for binding to the opioid receptors.

The investigation of these 5α,1'-methyleneoxy-6,7-benzomorphans may shed further light on the role of both the C ring and aromatic oxygenation in morphinoid systems.[20]

Chemistry

Treatment of dihydrocodeinone oxime 3.45 with thionyl chloride afforded 2 products as determined by TLC. The major product 3.46 was isolated by recrystallisation from methanol and is the secondary or 'abnormal' Beckmann product. The remaining compound proved extremely labile, decomposed on handling, and could not be isolated or characterised. In the absence of other evidence this may be the 'normal' Beckmann product, the 7 membered ring lactam 3.46b, (scheme 3.3a).



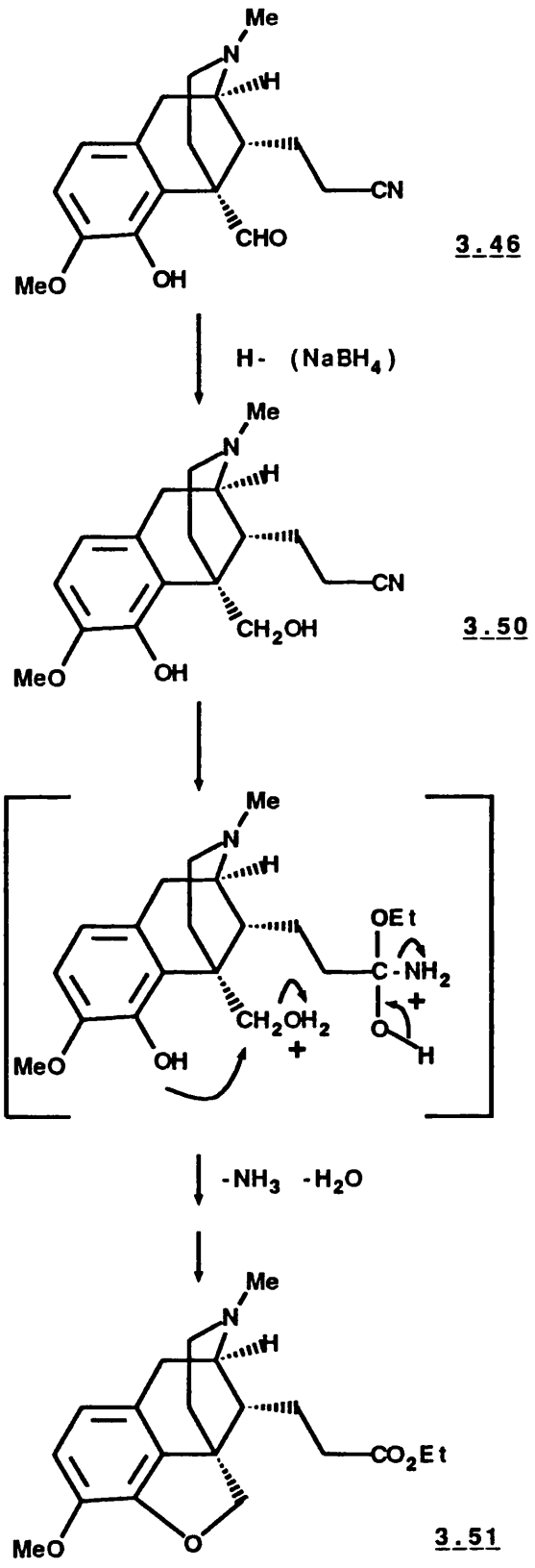
3.45

3.46b

3.46

SCHEME 3.3a

3.46 was eventually obtained in 30% yield after several crystallisations from methanol. Reduction of the aldehyde group in 3.46 with sodium borohydride in ethanol gave the corresponding alcohol 3.50. Alcoholysis of the nitrile group in 3.50 with anhydrous ethanol and concentrated H_2SO_4 not only produced the corresponding ester, but also, through protonation of the alcohol group and attack by the phenolic hydroxyl group, effected cyclisation of the furan ring to the 5α-furano derivative 3.51. This can be regarded as the key intermediate of the series of furanobenzomorphans (scheme 3.4).


Me
N
H
CN
CHO
MeO
OH
3.46
H- (NaBH4)
Me
N
H
CN
CH2OH
MeO
OH
3.50
Me
N
H
OEt
C-NH2
+
CH2OH2
+
O
H
MeO
OH
-NH3 -H2O
Me
N
H
CO2Et
MeO
O
3.51

SCHEME 3.4

The ^{1}H NMR spectrum of 3.51 showed the new furan ring methylene proton signal as an AB quartet centred at δ = 4.41 ppm (J=8Hz), (figure 3.2), c.f. -CH_2OH in 3.50 with δ = 4.0 ppm (figure 3.1).

Ester 3.51 was readily reduced in high yield to the alcohol 3.52 using lithium aluminium hydride (LAH) in THF. 3.52 was further reduced to 3.53 by modification of a previously published method.[21] Methyl triphenoxyphosphonium iodide in anhydrous THF converted 3.52 to the corresponding alkyl iodide which was not isolated but was reduced *in situ* to 3.53 with sodium cyanoborohydride (scheme 3.5). O-Demethylation of 3.53 was achieved with a solution of boron tribomide in chloroform[22]; 3.54 was obtained in high yield (scheme 3.6).

Acetylation of 3.54 with acetyl chloride in the presence of triethylamine gave 3.55 (scheme 3.7).

Preparation of the N-allyl and N-phenethyl derivatives, 3.57 and 3.58 respectively, was achieved *via* N-demethylation[23] of 3.54 followed by reaction of the resulting secondary amine 3.56, with the appropriate alkyl halide. Thus, reaction of 3.54 with 2,2,2-trichloroethylchloroformate and potassium carbonate in toluene gave the trichloroethylcarbamate ester, which hydrolysed under the influence of zinc and acetic acid to give 3.56 (scheme 3.8).

FIGURE 3.1

^{1}H 60 MHz NMR SPECTRUM OF 3.50 ($CDCl_3$ solvent, TMS ref.)

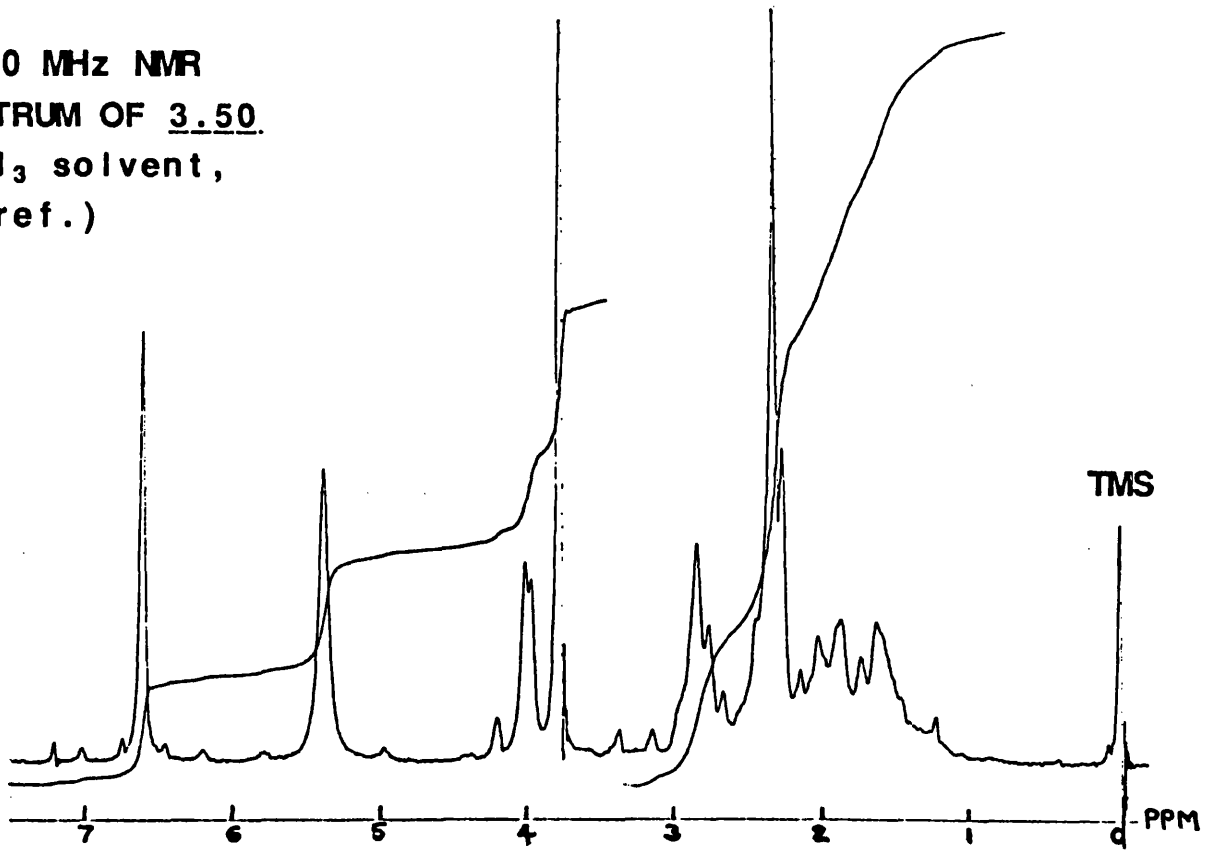
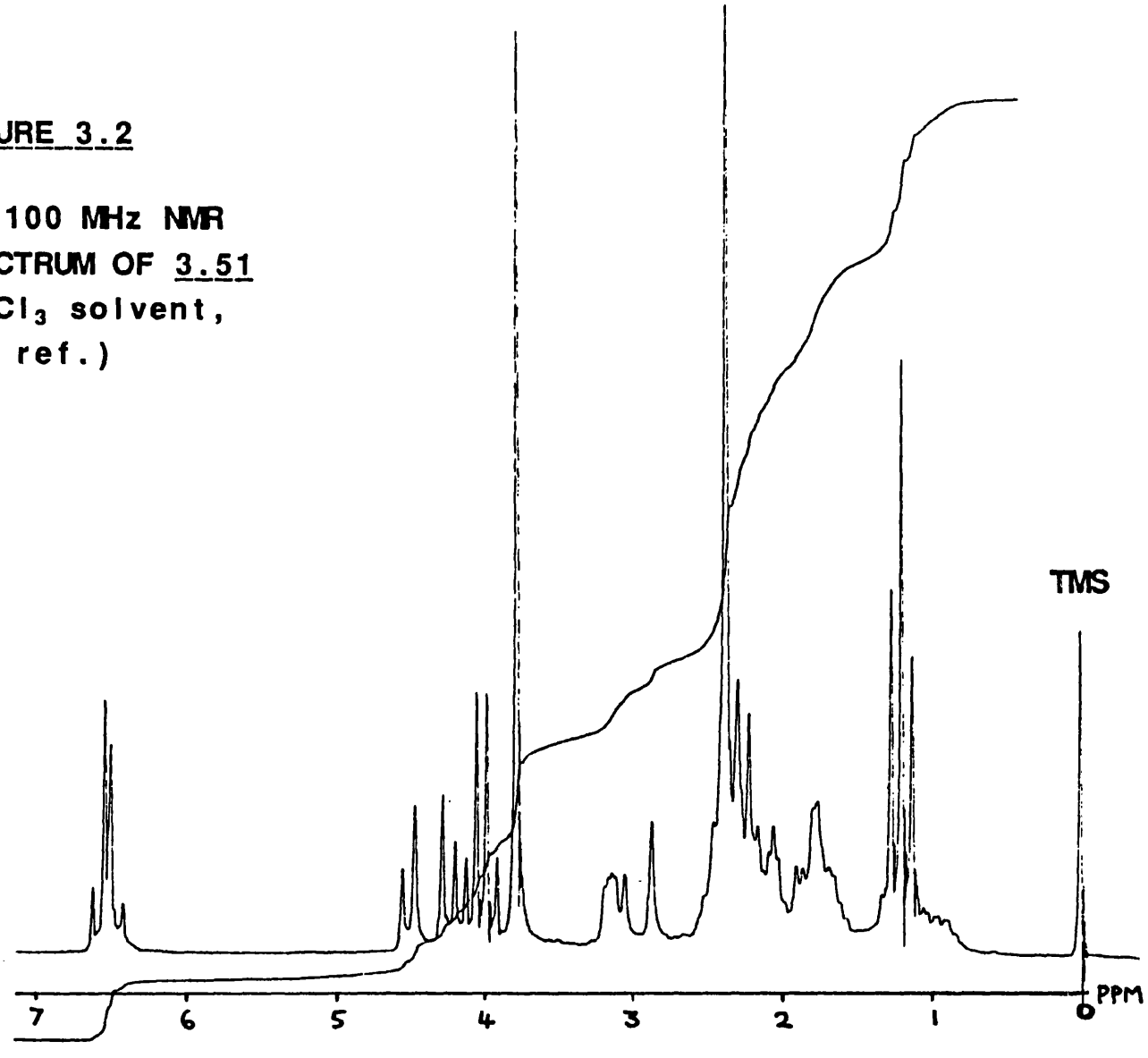
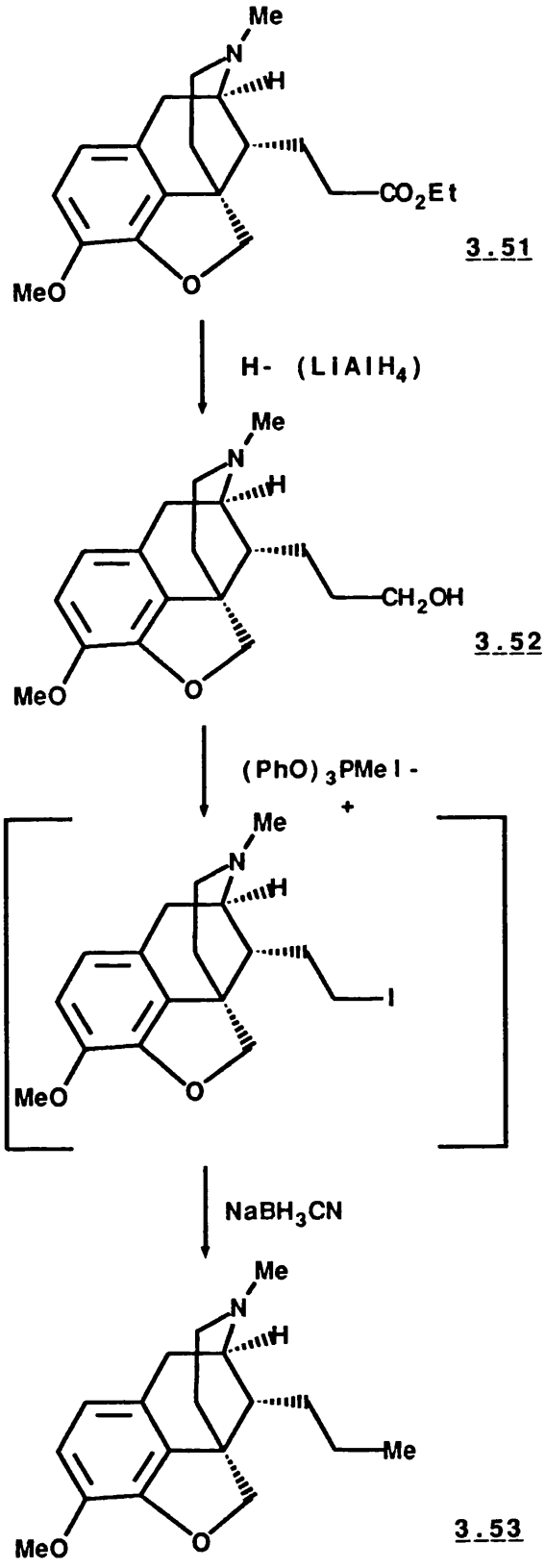


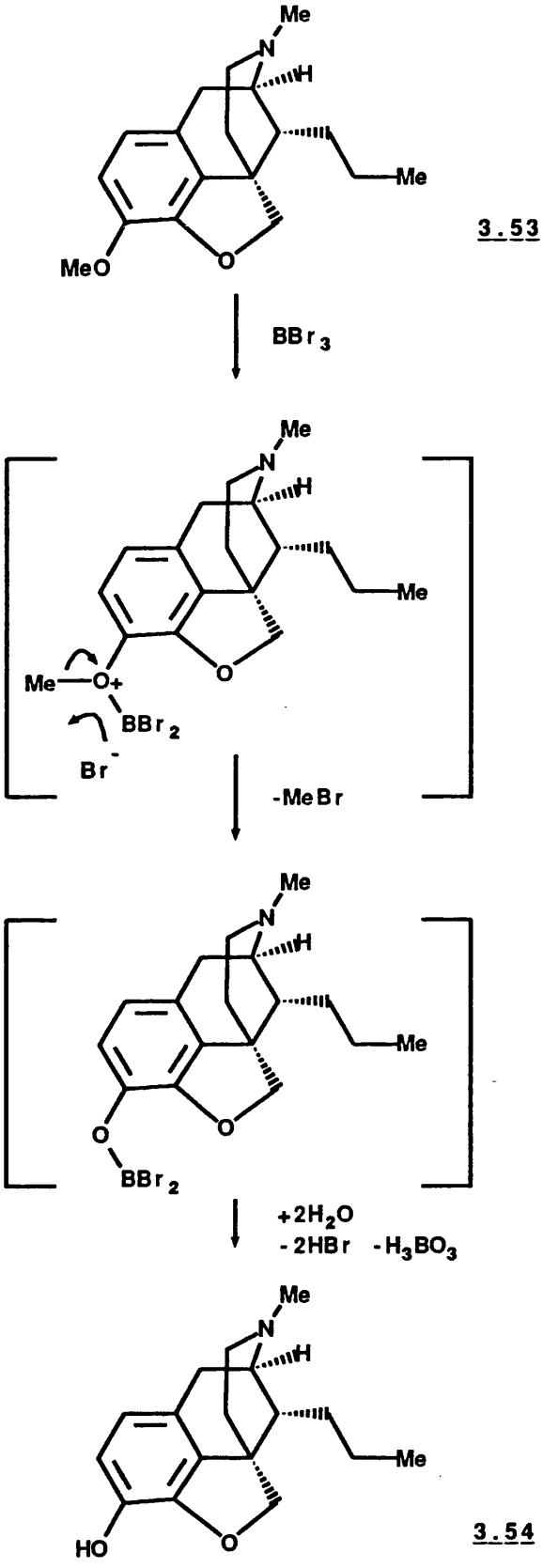
FIGURE 3.2

^{1}H 100 MHz NMR SPECTRUM OF 3.51 ($CDCl_3$ solvent, TMS ref.)

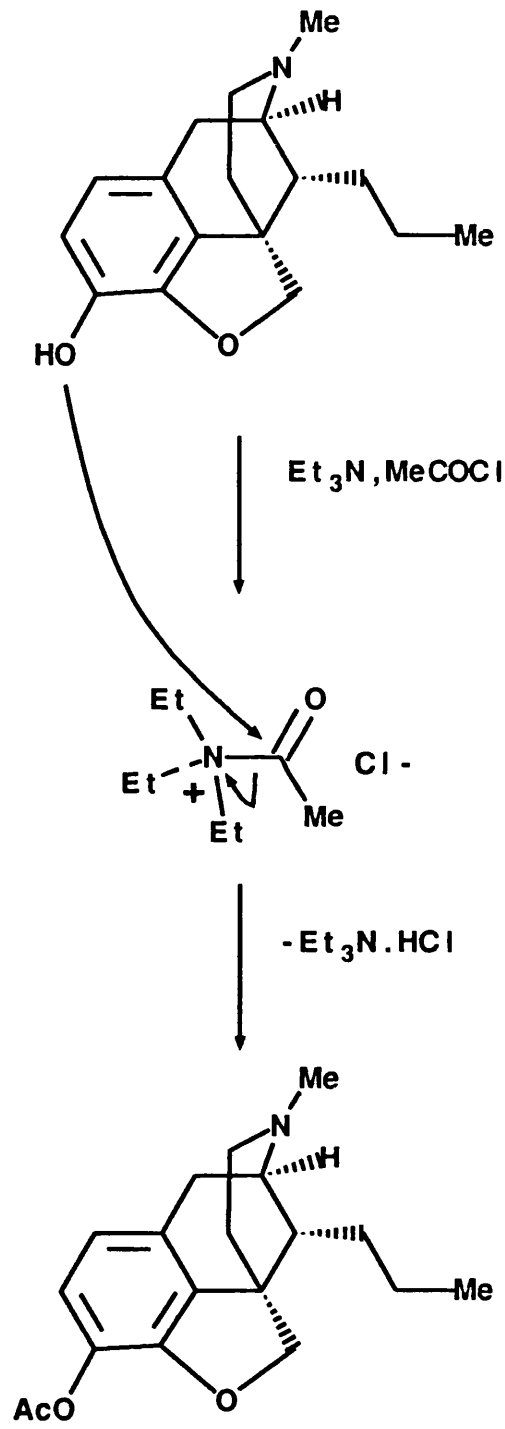



Me
N
H
CO2Et
MeO
O
3.51
H- (LiAlH4)
CH2OH
3.52
(PhO)3PMeI-
+
I
NaBH3CN
Me
3.53

SCHEME 3.5


Me
N
H
Me
MeO
O
3.53
BBr3
Me
N
H
Me
Me
O+
O
BBr2
Br-
-MeBr
Me
N
H
Me
O
O
BBr2
+2H2O
-2HBr -H3BO3
Me
N
H
Me
HO
O
3.54

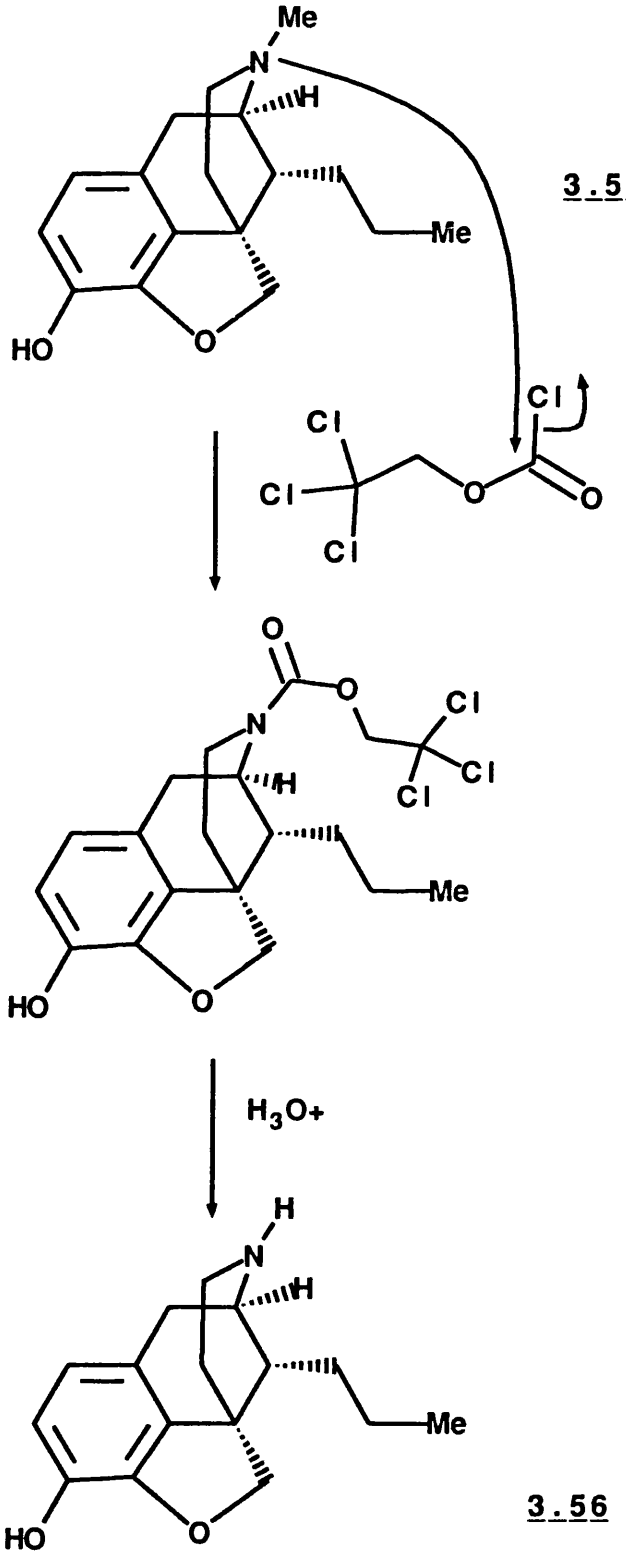
SCHEME 3.6



3.54

3.55

SCHEME 3.7

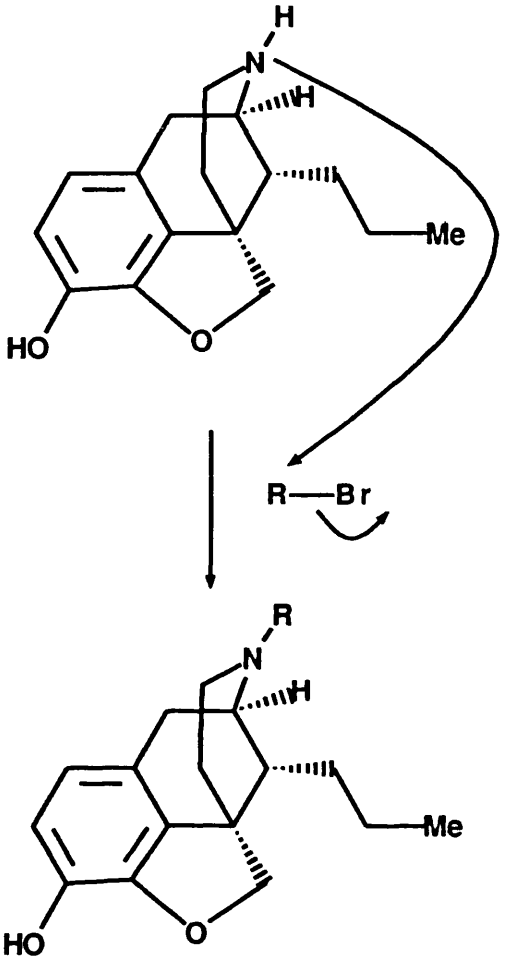

Me
N
H
Me
HO
O
3.54
Cl
Cl
Cl
Cl
Cl
O
O
O
N
H
Cl
Cl
Cl
Me
HO
O
H_3O+
H
N
H
Me
HO
O
3.56

SCHEME 3.8

Reaction of 3.56 with an excess of allyl bromide gave mixtures of N-allyl and N,O-diallyl material (scheme 3.9). Pure 3.57 was separated from the crude mixture by extraction of its sodium salt into aqueous sodium hydroxide solution. This procedure accounts for the low yield for the conversion.

Reaction of 3.56 with phenethyl bromide also required an excess of alkyl halide for satisfactory yields of the N-phenethyl compound 3.58 (scheme 3.9). This also led to substanial O-alkylation. Due to the poor solubility of the sodium salt of 3.58 in aqueous media, the separation technique for 3.57 failed.

However, yields of 3.58 were substantially increased by O-dealkylation of the crude product with boron tribomide.



3.56

3.57 R=allyl

3.58 R=CH_2CH_2Ph

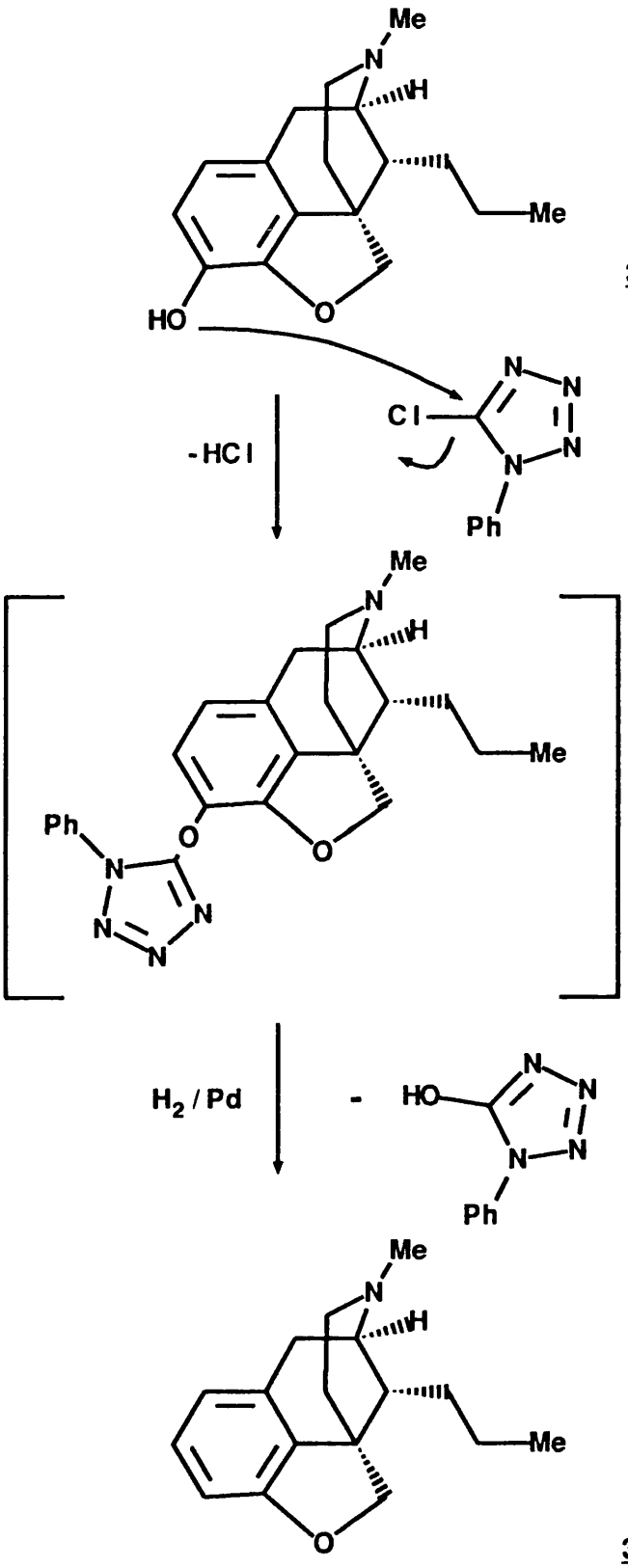
SCHEME 3.9

Reduction of the 5,1'-Furan Ring in 3.54

First, hydrogenolysis of the 2'-hydroxy group in 3.54 was achieved through conversion to its 2'-(1-phenyltetrazole) derivative, and subsequent cleavage by catalytic hydrogenation over a palladium catalyst[24] gave 3.59 (scheme 3.10). Ring opening of 3.59 was achieved using an excess of LAH in THF. Conventional work-up procedures had previously led to poor recovery of 3.60, but considerable improvement was obtained by addition of the crude reaction slurry to a stirred mixture of aqueous sodium carbonate and chloroform, followed by further chloroform extraction of the aqueous layer (see experimental section).

Structural assignment of 3.60 was supported by the loss of the furan (5') ring protons and the associated upfield resonance at δ = 1.8 ppm for the 5-methyl protons (figure 3.3).

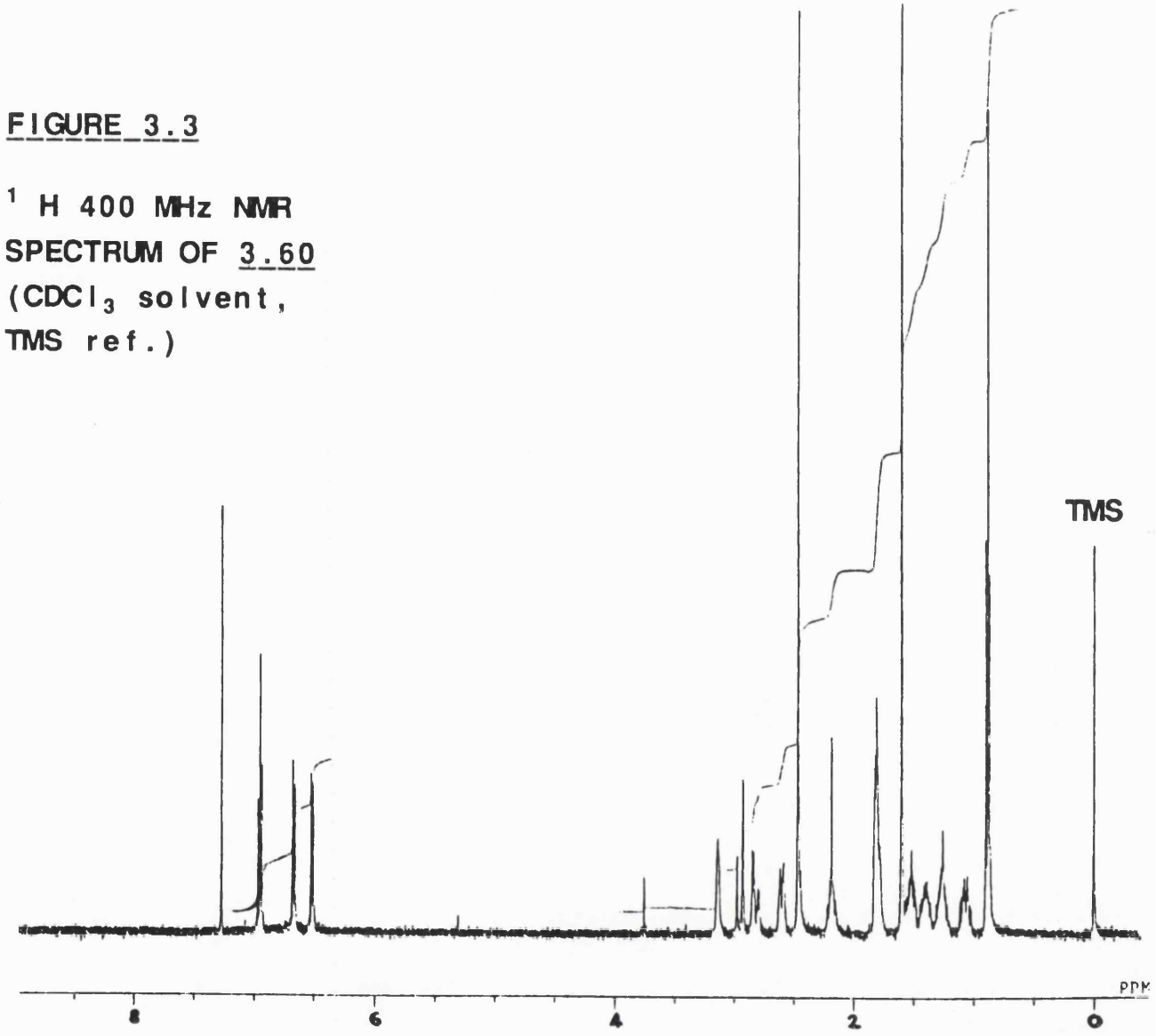
The 1'-methoxy derivative 3.61 was obtained in low yield by methylation of 3.60 with diazomethane in methanol/ether solution (scheme 3.11).

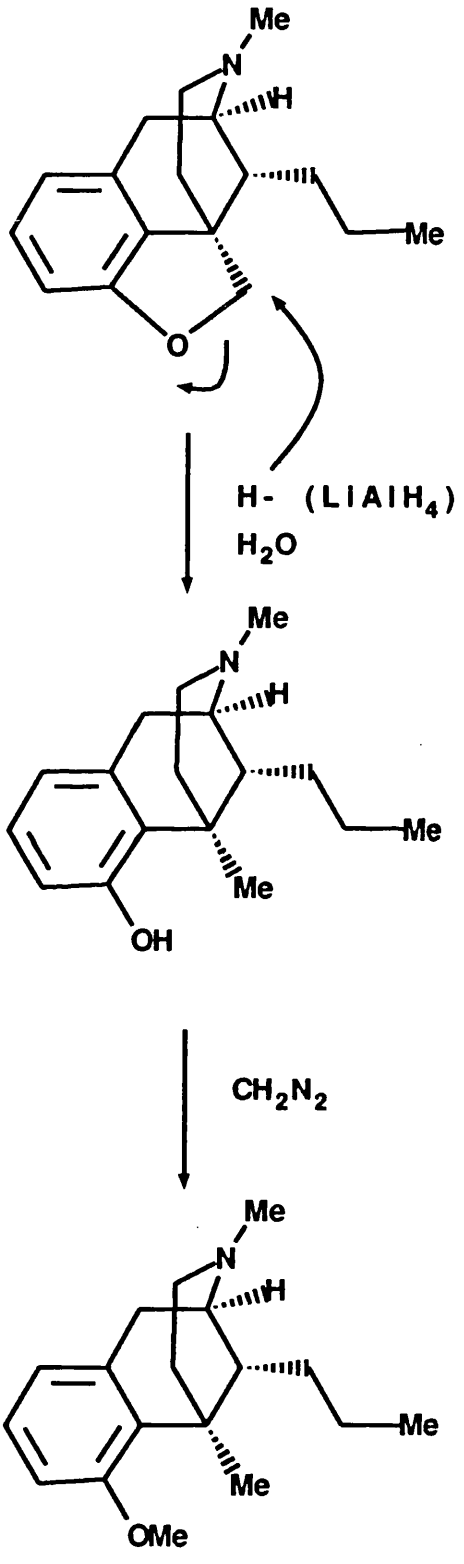

Me
N
H
Me
HO
O
3.54
N
N
Cl
N
N
Ph
-HCl
Me
N
H
Me
Ph
O
O
N
N
N
H_2 / Pd
-
HO
N
N
N
N
Ph
Me
N
H
Me
O
3.59

SCHEME 3.10

FIGURE 3.3

^{1}H 400 MHz NMR SPECTRUM OF 3.60 ($CDCl_3$ solvent, TMS ref.)





3.59

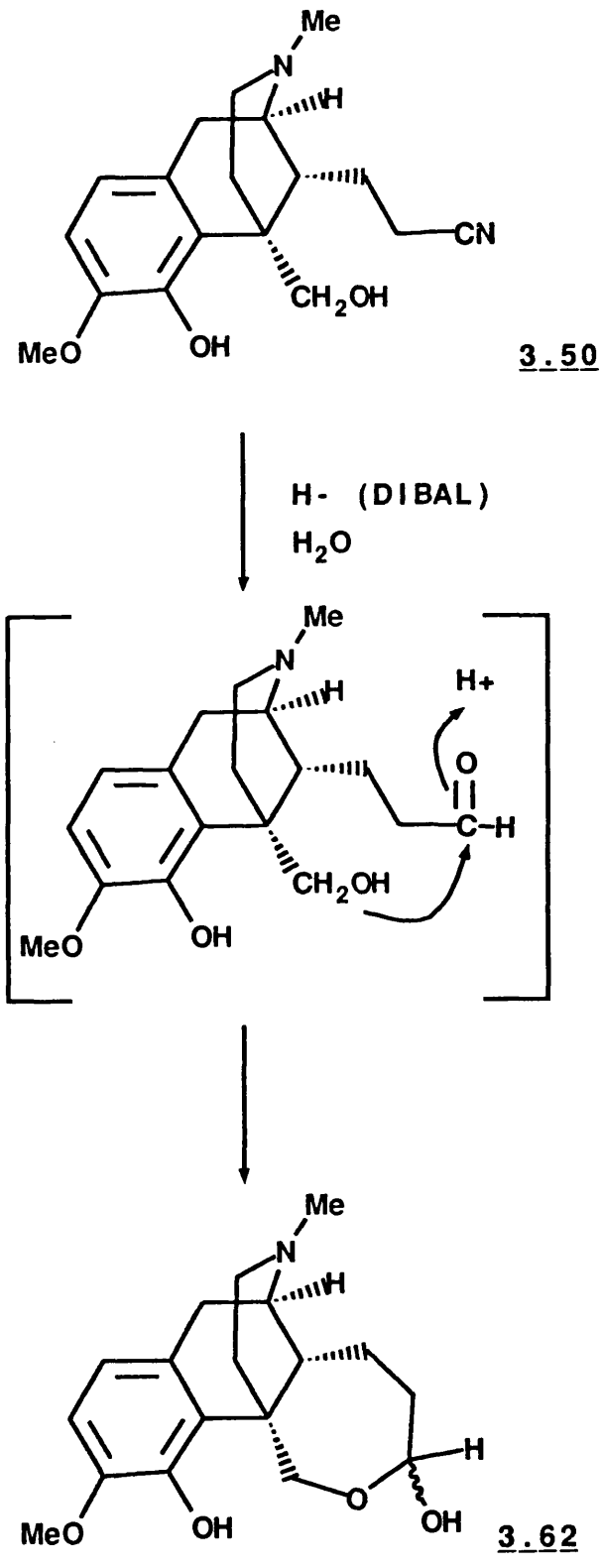
3.60

3.61

SCHEME 3.11

In addition to the above series of benzomorphans, a novel homo-oxa-derivative of N-methyl morphinan, hemiacetal 3.62, was obtained[25] *via* reduction of the nitrile group in 3.50 with the selective reducing agent, diisobutylaluminium hydride (DIBAL) (scheme 3.12).

The structure of 3.62 was supported by its ^{1}H and ^{13}C NMR spectra (figures 3.4 and 3.5 respectively) as well as by microanalytical data (table 3.5).


Me
N
H
CN
CH2OH
MeO
OH
3.50
H- (DIBAL)
H2O
Me
N
H
H+
O
C-H
CH2OH
MeO
OH
Me
N
H
H
O
OH
MeO
OH
3.62

SCHEME 3.12

FIGURE 3.4

^{1}H 60 MHz NMR SPECTRUM OF 3.62 ($CDCl_3$ solvent, TMS ref.)

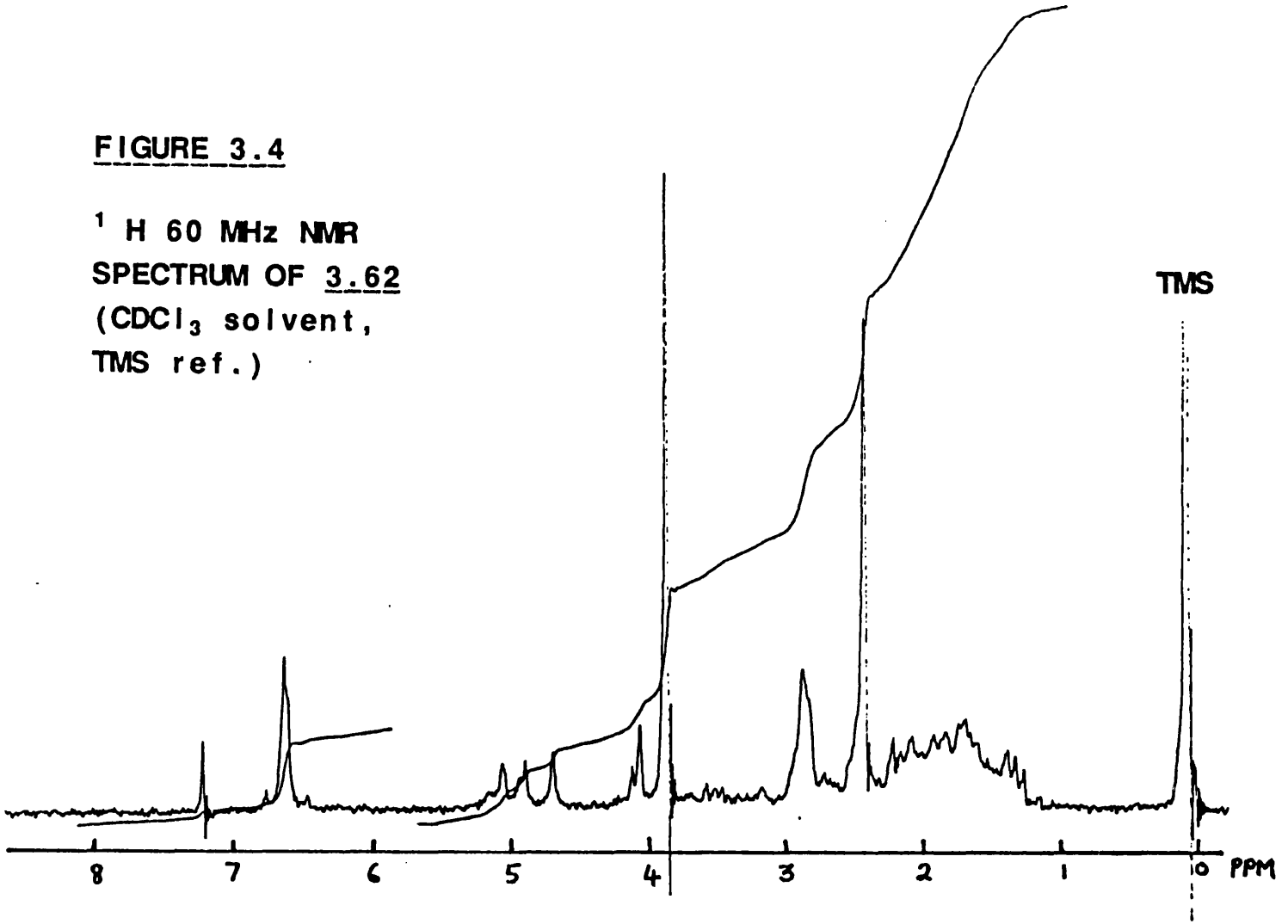
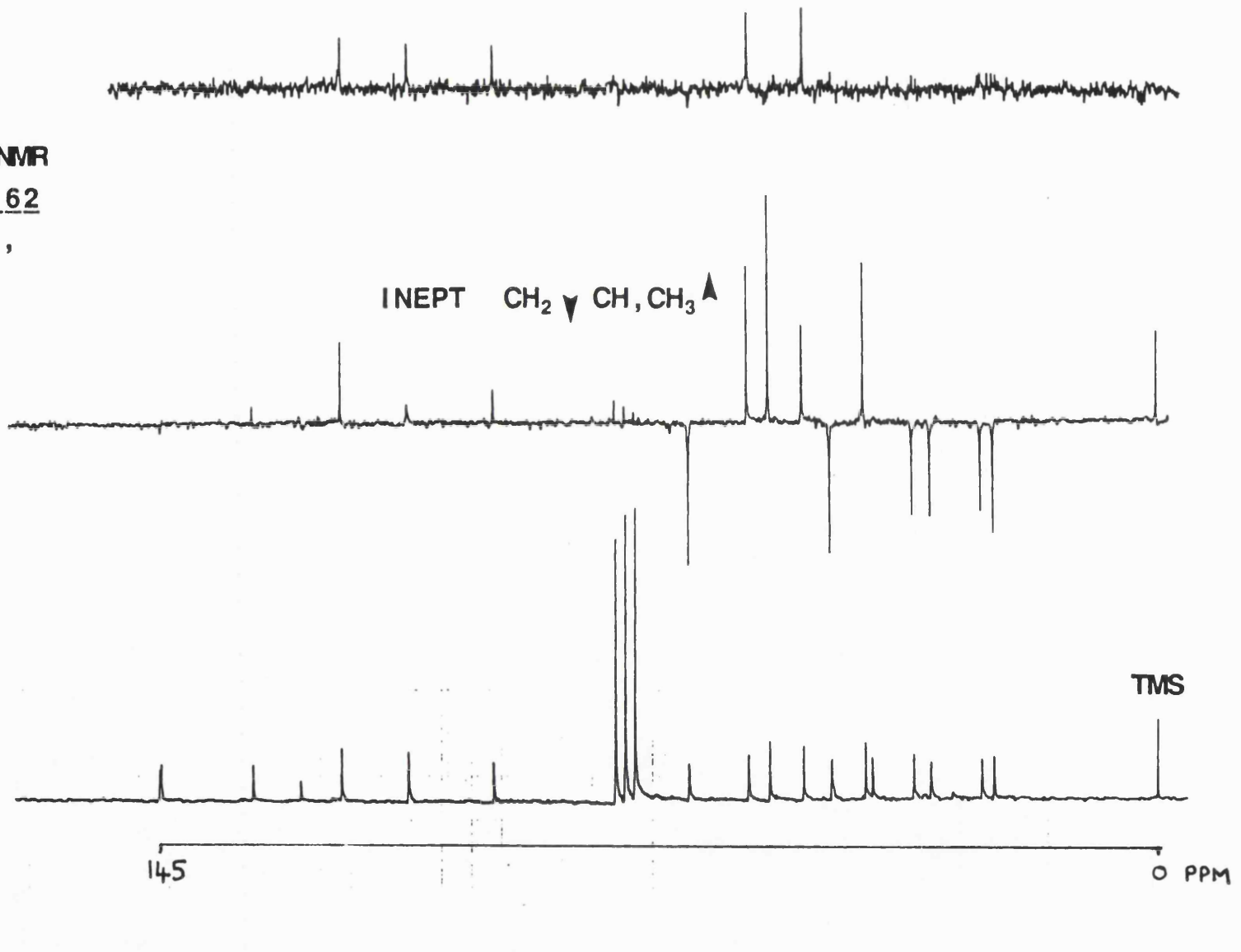


FIGURE 3.5

^{13}C 22.5 MHz NMR SPECTRUM OF 3.62 ($CDCl_3$ solvent, TMS ref.)



Discussion of Biological Results

Since (-)-2,5-dimethyl-2'-hydroxy-9α-propyl-6,7-benzomorphan (3.44) has been reported to show similar levels of analgesic potency to morphine and has also been demonstrated to lack a PDC in rhesus monkeys[15], similar levels of activity were expected in the 5α,1'-methyleneoxy-9α-propyl-6,7-benzomorphans (3.54 - 3.58).

The 2'-hydroxy derivative 3.54 showed a level of potency approximately two thirds that of morphine in the mouse hot plate test (MHP), with an ED_{50} of 1.8 mg/kg (table 3.3). 3.54 also showed the highest potency of the group in both the mouse tail flick (MTF) and paraphenylquinone writhing test (PPO), with ED_{50}s of 0.4 and 0.1 mg/kg respectively.

Masking of the phenolic OH by methyl, as in 3.53, or its removal as in 3.59, caused loss of activity in the MHP test. Although there are exceptions known, for example those previously mentioned (e.g. 3.28), this result is broadly in line with those of other 5,9-dialkyl-6,7-benzomorphans, where the non-phenolic derivatives are generally less potent; however masking of the 2' phenolic OH by an acetoxy group as in 3.55, or its removal, as in 3.59, also abolished analgesic activity.

Acetylation of the 2' position in morphinoid systems often enhances, rather than reduces, agonist activity (c.f. heroin and morphine).

TABLE 3.3 ANALGESIC ACTIVITIES OF 3.51-3.62

Compound[a]	MHP[b]	MTF[c]	PPO[d]	MTF[e]
3.51	IA[f] (50)	IA[f] (30)	g	IA[f] (30)
3.52	IA[f] (20)	IA[f] (10)	IA[f] (30)	
3.53	IA[f] (20)	8.1(2.3-28.2)	0.8(0.3-2.8)	IA[f] (30)
3.54	1.8(1.3-2.6)	0.4(0.2-0.8)	0.1(0.06-0.2)	IA[f] (30)
3.55	g	0.7(0.5-1.0)	0.2(0.1-0.3)	IA[f] (30)
3.57	IA[f] (20)	IA[f] (30)	g	0.4(0.1-1.0)
3.58	1.7(1.4-2.1)	1.4(0.9-2.4)	0.2(0.1-0.4)	IA[f] (30)
3.59	IA[f] (20)	20.7(14-30.1)	2.9(1.3-6.3)	IA[f] (30)
3.60	IA[f] (20)			
3.61	IA[f] (20)			
3.62	IA[f] (20)			
Morphine sulphate	1.2	5.8	0.23	
Codeine phosphate	9.3	14.5	1.1	
Naloxone				0.035

See over for key

KEY FOR TABLE 3.3

a : Compounds tested as hydrochloride salts in water

b : Mouse hot plate test (ED_{50} mg/kg)

c : Mouse tail flick test (ED_{50} mg/kg)

d : Phenylquinone writhing test (ED_{50} mg/kg)

e : Mouse tail flick antagonist assay vs morphine

f : IA=Inactive at the dose level indicated

g : Low level of activity exhibited

The 2'-hydroxy group therefore seems particularly necessary for MHP activity in these 5α,1'-methyleneoxy-6,7-benzomorphans.

The N-phenethyl derivative 3.58 showed significant activity in the MHP test, with an ED_{50} of 1.7mg/kg, a similar potency level to that of 3.54, although lower levels of activity were exhibited in the MTF and PPO tests. These results for 3.58 are against the general trend seen in other 6,7-benzomorphans were substitution of methyl by phenethyl on nitrogen generally increases activity.

The N-allyl derivative 3.57 was inactive as an analgesic agonist, but showed itself to be an antagonist of morphine (AD_{50} 0.4mg/kg: one tenth as active an antagonist as nalorphine).

Other Derivatives

The 1'-hydroxy and 1'-methoxy-5α-methyl-9α-propyl-6,7-benzomorphans 3.60 and 3.61 respectively, lacked analgesic activity in the MHP test as did hemiacetal 3.62. 3.61 might be regarded as stereochemically similar to the 5α,1'-methyleneoxy derivative 3.59 which was also inactive in the MHP test. The 1'-hydroxy group may be less stereochemically suited to bind to the receptor than the 2'-hydroxy group as in 3.54. Hemiacetal 3.62 also possesses 1'-hydroxy and 2'-methoxy substituents which, as in the previous examples, seem to be unsuitable for satisfactory receptor binding.

Experimental Section

Infra-red spectra were recorded on a Unicam SP1025 spectrometer.

Melting points (uncorrected) were taken on a Gallenkamp melting point apparatus.

^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer operating at 22.5 MHz. The multiplicity of the resonances was obtained by either off-resonance (partial ^{1}H coupling) spectra, or by INEPT (Insensitive Nuclei Enhanced by Polarisation Transfer) spectra in which the phase of the signal indicated the number of protons attached to each carbon atom.

^{1}H NMR spectra were recorded using JEOL JNM-PMX 60 SI, JEOL PS100 and JEOL GX400 spectrometers. NMR samples (as bases unless stated otherwise) were prepared in 5mm o.d. tubes as approximately 10% solutions in $CDCl_3$ (unless stated otherwise) with TMS as reference.

Mass spectra were recorded on a VG 7070E mass spectrometer operating at 70 eV (EI).

Optical Rotations were measured on an Optical Activity Ltd AA-10 polarimeter.

Elemental analyses were performed by Butterworths Laboratories Ltd., Middlesex.

Formulae and abbreviations as used in the experimental section

$CDCl_3$	Deuterochloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
D_2O	Deuterium Oxide
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
HCl	Hydrochloric Acid
H_2SO_4	Sulphuric Acid
K_2CO_3	Potassium Carbonate
MeOH	Methanol
Me_2CO	Acetone
$MgSO_4$	Magnesium Sulphate (anhydrous)
NaOH	Sodium Hydroxide
Na_2SO_4	Sodium Sulphate (anhydrous)
$NaHCO_3$	Sodium Bicarbonate
Pr^iOH	Isopropanol
THF	Tetrahydrofuran
TMS	Tetramethylsilane

'Solvent was removed' - denotes evaporation under reduced pressure using a rotary evaporator.

Dihydrocodeinone oxime (3.45)[26]

A stirred mixture of dihydrocodeinone (117.6g, 0.39 mol), hydroxylamine hydrochloride (70g, 1.0 mol), sodium acetate (41g, 0.5 mol) in water (2 L) was heated under reflux for 2 hours, then cooled and made alkaline by addition of 10% aqueous ammonia solution. The precipitated oxime was filtered, washed with water until washings were neutral, finally washed with EtOAc (400 ml) and dried under vacuum at 110°C for 4 hours to give 3.45 (121.8g, 99%) as a white solid. m.p. 262 - 264°C, (lit[26] m.p. 264 - 265°C).

EIMS m/z 314 (M+)

(-)-9α-(2-Cyanoethyl)-5α-formyl-1'-hydroxy-2'-methoxy-2-methyl-6,7-benzomorphan (3.46)[16]

Dihydrocodeinone oxime 3.45 (60g, 0.19 mol) was added in small portions to freshly distilled thionyl chloride (210 ml), stirred and maintained between -5° and -10°C. The resulting mixture was stirred at -5°C for 2 hours, then thionyl chloride removed under reduced pressure at below 30°C. Iced water (150 ml) was added slowly over 10 minutes, stirred vigorously for 30 minutes to induce precipitation and then left overnight at 2°C. The separated solid was filtered, washed with cold water (20 ml), then suspended in water (100 ml) and heated strongly until no more sulphur dioxide and hydrogen chloride was evolved. The filtrate was also heated to remove the bulk of sulphur dioxide and hydrogen chloride. The two solutions were separately basified with 10% aqueous ammonia solution and extracted with CH_2Cl_2 (3 x 200 ml), dried ($MgSO_4$) and solvent removed to give crude 3.46, 18.6g and 22.1g respectively. Repeated crystallisation from MeOH yielded 3.46 (18.2g, 30%) as colourless crystals, m.p. 195°C (lit[16] m.p. 190-1°C).
$[\alpha]_D^{20}$ -46° (c 1, 95% EtOH).

IR (KBr) 1740 cm^{-1} (C = O)

2270 cm^{-1} (C ≡ N)

^{1}H NMR	1.5 - 3.3	δ (m, 15 aliphatic H)
including	2.4	δ (s, 3H, NCH_3)
	3.85	δ (s, 3H, OCH_3)
	5.7	δ (brs, 1H, OH, exchanges with D_2O)
	6.7	δ (brs, 2H, 2 x ArH)
	9.65	δ (s, 1H, CHO)

^{13}C NMR — See table 3.4

Analysis — See table 3.5

(-)-9α-(2-Cyanoethyl)-1'-hydroxy-5α-hydroxymethyl-2'-methoxy-2-methyl-6,7-benzomorphan (3.50)

To a solution of sodium borohydride (8g) in absolute ethanol (800 ml) was added finely powdered 3.46 (29.5g, 0.094 mol) in small portions. After stirring at room temperature for 1 hour, the mixture was filtered, then made acidic with 2N HCl and the solvent removed to give a solid residue. This was dissolved in water (1 L) washed with Et_2O (3 x 200 ml; discarded), saturated with Na_2CO_3 and extracted with $CHCl_3$ (5 x 300 ml). The combined $CHCl_3$ extracts were dried ($MgSO_4$) and solvent removed to give 3.50 (26.2g, 88%) as a colourless solid. m.p. 80°C. TLC (MeOH:aq.ammonia 50:1) showed the product to be a single component. This product, and its hydrochloride and oxalate salts, could not be crystallised.

EIMS m/z calc'd 316.1787

found 316.1786

IR (KBr) 2270 cm^{-1} (C ≡ N)

^1H NMR 1.2 - 3.0 δ (m, 15 aliphatic H)

including 2.35 δ (s, 3H, NCH_3)

3.8 δ (s, 3H, OCH_3)

4.0 δ (ABq, J=8Hz, 2H, $C\underline{H}_2OH$)

5.4 δ (brs, 2H, 2 x OH, exchanges with D_2O)

6.6 δ (s, 2H, 2 x ArH)

^{13}C NMR See table 3.4.

(-)-9α-(2-Ethoxycarbonyl)ethyl-5α,1'-methyleneoxy-2'-methoxy-2-methyl-6,7-benzomorphan (3.51)

To a solution of 3.50 (13.5g, 0.043 mol) in 'super dry' ethanol (500 ml) was cautiously added conc H_2SO_4 (200 ml). The solution was refluxed for 4 hours then cooled, basified with Na_2CO_3 solution and extracted with $CHCl_3$ (5 x 300 ml). The combined organic layers were dried ($MgSO_4$) and solvent removed to give crude 3.51 (12.9g, 87%) as a viscous yellow oil. The oxalate salt crystallised from Me_2CO-EtOH as yellow needles, m.p. 167-170°C. The hydrochloride crystallised from EtOAC - EtOH as colourless needles, m.p. 102-3°C.

The liberated free base gave $[\alpha]_D^{20}$ - 51° (c 1, 95% EtOH)

EIMS m/z 345 (M+)

IR ($CHCl_3$) 1735 cm^{-1} (C = O)

^1H NMR 0.8 - 2.6 δ (m, 16 aliphatic H)

including 1.2 δ (t, J=8Hz, 3H, $CH_2\underline{CH_3}$)

and 2.4 δ (s, 3H, NCH_3)

3.1 δ (m, 2H, NCH_2)

3.8 δ (s, 3H, OCH_3)

4.05 δ (q, J=8Hz, 2H, $C\underline{H_2}CH_3$)

4.4 δ (ABq, J=8Hz, OCH_2C)

6.6 δ (ABq, J=8Hz, 2H, 2 x ArH)

^{13}C NMR See table 3.4

Analysis See table 3.5

(-)-9α-Hydroxypropyl-5α,1'-methyleneoxy-2'-methoxy-2-methyl-6,7-benzomorphan (3.52)

To a suspension of LAH (7g) in anhydrous THF (200 ml) was slowly added a solution of 3.51 (13g, 0.038 mol) in anhydrous THF (500 ml). After stirring for 1 hour at 20°C, a saturated solution of Na_2CO_3 (12 ml) was added slowly dropwise and the mixture diluted with $CHCl_3$ (1 L), dried ($MgSO_4$) and filtered. Removal of solvent gave 3.52 (11.2g, 98%) as a viscous yellow oil. The hydrochloride crystallised from Et_2O-EtOH as white needles, m.p. 190-2°C.

The liberated free base gave $[\alpha]_D^{20}$ -43° (c 1, 95% EtOH).

^1H NMR

0.7 - 2.6 δ (m, 15 aliphatic H)
2.4 δ (s, 3H, NCH_3)
3.1 δ (m, 2H, NCH_2)
3.6 δ (br t, J=7Hz, 2H, CH_2OH)
3.9 δ (s, 3H, OCH_3)
4.05 δ (br s, 1H, OH, exchanges with D_2O)
4.5 δ (ABq, J=8Hz, 2H, OCH_2C)
6.8 δ (ABq, J=8Hz, 2H, 2 x ArH)

^{13}C NMR See table 3.4

Analysis See table 3.5

(-)-5α,1'-Methylenoxy-2'-methoxy-9α-propyl-6,7-benzomorphan (3.53)

In a dry box under a nitrogen atmosphere, methyltriphenoxy phosphonium iodide (20g, 0.044 mol) was added to a solution of 3.52 (4.8g, 0.016 mol) in anhydrous THF (150 ml), followed by sodium cyanoborohydride (5g). The mixture was removed from the dry box, then heated to 50-60°C for 3 hours, cooled, basified with Na_2CO_3 solution and extracted with $CHCl_3$ (3 x 200 ml). The organic layers were combined and solvent removed to give a crude yellow oil. This was dissolved in 6M HCl (300 ml), washed with Et_2O (3 x 300 ml; discarded) basisfied with Na_2CO_3 and extracted with Et_2O (5 x 200 ml). The combined ethereal layers were dried ($MgSO_4$) and solvent removed to give 3.53 (3.3g, 72%) as a viscous yellow oil. Purification was effected by vacuum distillation at 130°C/0.01mmHg (decomposition starts @ ~ 140°C);3.53 was obtained as a colourless viscous oil (yield 43%). The hydrochloride crystallised from EtOAc-EtOH as colourless needles, m.p. 222-4°C.

The liberated free base gave $[\alpha]_D^{20}$ -51° (c 0.96, 95% EtOH)

EIMS m/z 287 (M+)

^{1}H NMR

0.85 δ (br t, J=8Hz, 3H, $CH_2CH_2CH_3$)

1.25 - 2.5 δ (m, 10 aliphatic H)

including

2.4 δ (s, 3H, NCH_3)

3.1 δ (m, 2H, NCH_2)

3.82 δ (s, 3H, OCH_3)

4.4 δ (ABq, J=8Hz, 2H, OCH_2C)

6.62 δ (ABq, J=8Hz, 2H, 2 x ArH)

^{13}C NMR See table 3.4

Analysis See table 3.5

(-)-8-Hydroxy-5α,1'-methyleneoxy-2-methyl-9α-propyl-6,7-benzomorphan (3.54)

A solution of 3.53 (3.8g, 0.013 mol) in purified $CHCl_3$ (150 ml) was added over 5 minutes to a stirred solution of boron tribomide (34.45g, 0.138 mol) in purified $CHCl_3$ (150 ml). After stirring for 1 hour at 20°C, the mixture was poured on to a stirred mixture of ice (200g) and concentrated aqueous ammonia (50 ml). The two layers were seperated and the aqueous layer further extracted with $CHCl_3$ (2 x 200 ml). The combined organic layers were dried ($MgSO_4$) and solvent removed to give 3.54 (3.0g, 83%) as a pale brown solid. This crystallised from Me_2CO as colourless prisms, m.p. 180-1°C. The hydrochloride crystallised from EtOAc-EtOH, m.p. 172-4°C.

The liberated free base gave $[\alpha]_D^{20}$ -59° (c 1, 95% EtOH)

EIMS m/z 273 (M+)

^1H NMR 0.8 - 2.8 δ (m, 18 aliphatic H)

including 2.4 δ (s, 3H, NCH_3)

3.1 δ (m, 2H, NCH_2)

4.25 δ (ABq, J=8Hz, 2H, OCH_2C)

6.45 δ (ABq, J=8Hz, 2H, 2 x ArH)

7.5 δ (br s, 1H, OH, exchanges with D_2O)

^{13}C NMR See table 3.4

Analysis See table 3.5

(-)-8-Acetoxy-5α,1'-methyleneoxy-2-methyl-9α-propyl-6,7-benzomorphan (3.55)

To a solution of 3.54 (0.8g, 0.003 mol) in anhydrous THF (40 ml) was added triethylamine (4 ml) followed by dropwise addition of acetyl chloride (4 ml). The mixture was stirred at 20°C for 30 minutes, then filtered and solvent removed to give a crude residue. This was taken up in 1M HCl (50 ml), washed with Et_2O (3 x 50 ml; discarded) basified with $NaHCO_3$ and extracted with Et_2O (3 x 50 ml). The combined ethereal extracts were dried ($MgSO_4$) and solvent removed to give 3.55 (0.6g, 65%) as a pale yellow oil. The hydrochloride crystallised from Et_2O-EtOAc as needles, m.p. 144-8°C.

The liberated free base had $[\alpha]_D^{20}$ -52° (c 1, 95% EtOH)

EIMS m/z 315 (M+)

^1H NMR 0.7 - 2.5 δ (m, 19 aliphatic H)

including 2.25 δ (s, 3H, $OCOCH_3$)

and 2.4 δ (2, 3H, NCH_3)

3.0 δ (m, 2H, NCH_2)

4.45 δ (ABq, J=8Hz, 2H, OCH_2C)

6.58 δ (ABq, J=8Hz, 2H, 2 x ArH)

^{13}C NMR See table 3.4

Analysis See table 3.5

(-)-2'-Hydroxy-5α,1'-methyleneoxy-9α-propyl-6,7-benzomorphan (3.56)

A mixture of 3.54 (1.3g, 0.0048 mol), freshly distilled 2,2,2-trichloroethylchloroformate (7.4 ml, 0.023 mol), anhydrous K_2CO_3 (6g) and anhydrous toluene (130 ml) was refluxed for 65 hours. The cooled mixture was filtered, solvent removed, and excess 2,2,2-trichloroethylchloroformate removed by distillation under reduced pressure (100°C @ 0.5 mmHg). The residual oil obtained was largly the corresponding N,O-di (trichloroethyloxycarbonyl) derivative. This was dissolved in 90% acetic acid (87 ml); zinc dust (4.3g) was added and the mixture stirred vigorously at 20°C for 16 hours. The mixture was filtered, basified with Na_2CO_3 and extracted with $CHCl_3$ (3 x 100 ml). The combined extracts were dried ($MgSO_4$) and solvent removed to give 3.56 (1g, 81%) as a pale yellow oil. This was used for subsequent reactions without further purification.

(-)-2-Allyl-2'-hydroxy-5α,1'-methyleneoxy-9α-propyl-6,7-benzomorphan (3.57)

A mixture of crude 3.56 (1g, 0.004 mol), allyl bromide (3.22g, 0.027 mol), anhydrous K_2CO_3 (2g) and $CHCl_3$ (75 ml) was heated at 60°C for 3 hours. The cooled mixture was filtered and solvent removed to give a crude yellow oil (1.1g). This was taken up in 2M NaOH (100ml) and washed with Et_2O (3 x 100 ml). The combined ethereal layers were extracted with 2M NaOH (50 ml). The combined aqueous layers were acidified with dilute HCl, washed with Et_2O (3 x 100ml; discarded) basified with 10% aqueous ammonia solution and extracted with Et_2O (5 x 100 ml). The combined ethereal layers were dried ($MgSO_4$) and solvent removed to give 3.57 (0.2g, 14%) as a colourless solid, m.p. 135-137°C. The hydrochloride crystallised from Me_2CO-EtOH-Et_2O, and had m.p. 245-6°C.

The liberated free base gave $[\alpha]_D^{20}$ -90° (c 1, 95% EtOH)

^{1}H NMR

0.7 - 3.5 δ (m, 15 aliphatic H)

4.18 δ (ABq, J=8Hz, 2H, OCH_2C)

4.8 - 5.4 δ (m, 2H, CH = $C\underline{H}_2$)

5.6 - 6.1 δ (m, 1H, $C\underline{H}$ = CH_2)

6.5 δ (ABq, J=8Hz, 2H, 2 x ArH)

7.65 δ (br s, 1H, OH, exchanges with D_2O)

^{13}C NMR — See table 3.4

Analysis — See table 3.5

(-)-2'-Hydroxy-5α,1'-methyleneoxy-2-phenethyl-9α-propyl-6,7-benzomorphan (3.58)

A mixture of crude 3.56 (0.6g, 0.0023 mol) anhydrous ethanol (15 ml), phenethyl bromide (0.94g, 0.0051 mol) and anhydrous K_2CO_3 (1g) was refluxed for 8 days. The cooled mixture was filtered and solvent removed to give a semi-solid residue (0.95g). This was dissolved in 6M HCl (100 ml), washed with Et_2O (3 x 100 ml; discarded), basified with Na_2CO_3 and extracted with Et_2O (5 x 100 ml). The combined ethereal extracts were dried ($MgSO_4$) and solvent removed to give 0.7g of largely N,O-dialkylated product. This was dissolved in purified $CHCl_3$ and added to a stirred solution of boron tribromide (12.5g, 0.05 mol) in purified $CHCl_3$ (100 ml). The mixture was stirred at 20°C for 5 hours then poured into a stirred mixture of ice (100g) and concentrated aqueous ammonia (20 ml). The 2 layers were separated and the aqueous layer further extracted with $CHCl_3$ (2 x 100 ml). The combined organic layers were dried ($MgSO_4$) and solvent removed to give crude 3.58 (0.6g) as a light brown solid. This was chromatrographed on silica gel (8g) using $CHCl_3$ as eluant. 3.58 (0.2g, 24%) was obtained as a light brown solid, m.p. 87-90°C. The hydrochloride crystallised from Me_2CO as needles, m.p. 270-5°C (dec).

The liberated free base gave $[\alpha]_D^{20}$ -68° (c 1, 95% EtOH)

^{1}H NMR 0.8 - 3.6 δ (m, 19 aliphatic H)

including 3.0 δ (m, 2H, CH_2Ph)

4.35 δ (ABq, J=8Hz, 2H, OCH_2C)

6.65 δ (ABq, J=8Hz, 2H, 2 x ArH)

7.15 δ (s, 5H, 5 x ArH)

7.45 δ (br s, 1H, OH, exchanges with D_2O)

^{13}C NMR See table 3.4

Analysis See table 3.5

(-)-5α,1'-Methyleneoxy-2-methyl-9α-propyl-6,7-benzomorphan (3.59)

A mixture of 3.54 (3.6g, 0.0132 mol), 5-chloro-1-phenyl-1H-tetrazole (2.17g, 0.015 mol) and anhydrous K_2CO_3 (3.6g) in anhydrous acetonitrile (150 ml) was refluxed for 48 hours. The cooled mixture was filtered and solvent removed to give a crude residual oil. This was hydrogenated in a Parr apparatus at 200 psi and 60°C for 3 days over 5% palladium on carbon (5g). Filtration of catalyst and removal of solvent gave a crude residue which was partitioned between EtOAc (200 ml) and 2N NaOH (100 ml). The aqueous layer was separated and further extracted with EtOAc (2 x 100 ml). The combined acidic layers were washed with Et_2O (2 x 100 ml; discarded), basified with Na_2CO_3 and extracted with Et_2O (5 x 200 ml). The combined ethereal layers were dried ($MgSO_4$) and solvent removed to give 3.59 (3g, 88%) as a yellow solid. The oxalate crystallised from EtOAc-EtOH and had m.p. 139-40°C. The hydrochloride crystallised from EtOAc-EtOH and had m.p. 205-7°C. The liberated free base gave $[\alpha]_D^{20}$ - 100° (c 0.5, 95% EtOH).

^{1}H NMR 0.8 - 3.25 δ (m, 18 aliphatic H)

including 2.4 δ (s, 3H, NCH_3)

4.18 δ (ABq, J=8Hz, 2H, OCH_2C)

6.45 - 7.2 δ (m, 3H, 3 x ArH)

^{13}C NMR See table 3.4

Analysis See table 3.5

(-)-1' -Hydroxy-2,5α-dimethyl-9α-propyl-6,7-benzomorphan (3.60)

To a stirred mixture of LAH (1.8g) in anhydrous THF (75ml) was added a solution of 3.59 (0.9g, 0.0035 mol) in anhydrous THF (75 ml) and the mixture heated under reflux for 3 days. The cooled mixture was added dropwise to a stirred mixture of saturated aqueous Na_2CO_3 (200 ml) and $CHCl_3$ (500 ml). The organic layer was separated and further extracted with $CHCl_3$ (2 x 200 ml). The combined organic layers were dried ($MgSO_4$) and solvent removed to give 3.60 (0.84g, 93%) as a yellow semi solid. This crystallised from EtOAc-Petroleum Ether (60-80°C) as white crystals, m.p. 208-210°C. $[\alpha]_D^{20}$ -50° (c 0.5, MeOH).

The hydrochloride crystallised from EtOAc-EtOH and had m.p. 155-158°C.

^{1}H NMR (DMSO-d^6)

0.7 - 1.8	δ	(m, 16 aliphatic H)
2.25	δ	(s, 3H, NCH_3)
2.75	δ	(m, 2H, NCH_2)
6.5 - 6.9	δ	(m, 3H, 3 x ArH)
8.8	δ	(br s, 1H, OH)

^{13}C NMR See table 3.4

Analysis See table 3.5

(-)-2,5α-Dimethyl-1'-methoxy-9α-propyl-6,7-benzomorphan (3.61)

To a stirred solution of 3.60 (0.83g, 0.0032 mol) in anhydrous MeOH (10 ml), at 0°C, was slowly added a solution of diazomethane (~6g) in Et_2O over 2 hours. After the end of the addition the solution was stirred for a further 6 hours at 0°C, then allowed to warm to room temperature overnight. Remaining solvent was then removed to give an orange semi-solid residue. This was taken up in Et_2O, filtered and filtrate evaporated to yield an orange/yellow semi-solid residue. This was taken up in petroleum ether (30-40°C) and cooled to -78°C. After 1 hour at this temperature the mixture was filtered and filtrate evaporated to give crude 3.61 (0.23g). This was chromatographed on silica gel (10g) using toluene:dioxan:EtOH:aqueous ammonia (50:40:5:1) as eluant. 3.61 (0.09g, 10%) was obtained as a yellow oil. The oxalate crystallised from Me_2CO and had m.p. 50°C.

The liberated free base gave $[\alpha]_D^{20}$ -12° (c 1, Me_2CO)

EIMS m/z 273 (M+)

^1H NMR
0.7 - 2.2 δ (m, 16 aliphatic H)
2.42 δ (s, 3H, NCH_3)
2.5 - 3.5 δ (m, 2 aliphatic H)
3.82 δ (s, 3H, OCH_3)
6.5 - 7.4 δ (m, 3H, 3 x ArH)

^{13}C NMR See table 3.4

(No C,H,N data available)

(-)-4,6-Dihydroxy-5-homo-5a-oxa-N-methylmorphinan (3.62)[25]

To a solution of 3.50 (0.11g, 0.0035 mol) in freshly distilled THF (20 ml) was added diisobutylaluminium hydride in toluene (2 ml of a 1.5M solution). After stirring the mixture for 2 hours at 20°C, a saturated solution of ammonium chloride (10 ml) was added and the mixture was brought to greater than pH9 by the addition of Na_2CO_3 solution. The aqueous layer was then continuously extracted for 24 hours with $CHCl_3$. Drying of the combined organic layers with $MgSO_4$ followed by removal of solvent, gave crude 3.62 as a pale yellow solid, which was chromatographed on silica gel (2.5g), using EtOH as eluant. 3.62 (0.03g, 27%) was obtained as a colourless solid which crystallised from Me_2CO, m.p. 149°C. The hydrochloride crystallised from EtOAc-EtOH and had m.p. 150°C.

The liberated free base gave $[\alpha]_D^{20}$ -20°C (c 0.2, 95% EtOH).

EIMS m/z 319 (M+)

IR (KBr) 1605 cm^{-1} (weak) (Ar-H)
3420 cm^{-1} (broad) (O-H)

^{1}H NMR
1.3 - 2.2 δ (m, 10 aliphatic H)
2.36 δ (s, 3H, NCH_3)
2.80 δ (m, 2H, NCH_2)
3.80 δ (s, 3H, OCH_3)
4.05 δ (m, 1H, C<u>H</u>OH)
4.6 - 5.1 δ (m, 2H, C<u>H</u>$_2$OCHOH)
6.6 δ (ABq, J=8Hz, 2H, 2 x ArH)

^{13}C NMR — See table 3.4

Analysis — See table 3.5

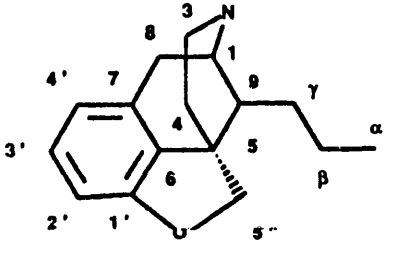
TABLE 3.4 ^{13}C NMR DATA OF 3.46-3.62

Compound[a]	C_α	C_4	C_β	C_8	C_3	C_α	C_1	C_9	C_5	$C_{5'}$	N-CH3	C_2"	C_1'	C_2"	C_3'	C_4'	C_6'	C_7'			
3.46	21.8	15.4	23.9	29.9	46.2	119.1	55.2	44.4	49.1	198.7	42.6	56.1	142.9	145.0	119.1	110.4	121.8	129.3			
3.50	23.2[b]	15.5	23.7[b]	33.6	46.5	119.9	55.1	46.5	41.3	70.0	42.6	56.1	143.9	145.5	119.0	109.2	124.8	130.7			
3.51	19.3	32.3	22.6	36.5	46.7	172.9	58.1	43.0	44.0	80.9	42.2	56.3	142.3	145.9	113.4	118.8	126.9	129.7	$CO_2\underline{C}H_2$ 60.3	$CH_2\underline{C}H_3$ 14.1	
3.52	19.3	30.7	23.7	36.4	46.8	62.1	58.2	42.9	44.0	81.0	42.2	56.4	142.6	145.8	113.2	118.6	127.0	130.0			
3.53	19.4	20.9	29.9	36.7	47.0	14.3	58.4	43.1	44.2	81.2	42.5	56.4	142.3	145.9	113.1	118.6	127.4	130.3			
3.54	19.7	20.7	29.9	35.9	47.0	14.4	58.2	42.7	44.1	80.9	41.7		139.1	145.0	117.0	119.0	125.5	129.9			
3.55[c]	19.8	20.1[b]	20.7[b]	36.6	46.7	13.9	58.1	42.3	44.3	81.4	42.6		[a]131.5	148.1	117.5	116.8	130.8[b]	132.4[b]	CO 168.8	$CO\underline{C}H_3$ 20.1[b]	
3.57	20.1	20.6	29.8	35.5	44.4	14.3	55.9	41.2	44.9	80.8			138.6	144.7	116.8	118.8	125.4	129.8	N-CH_2 58.0	CH= 134.6	$=CH_2$ 118.2
3.58	20.5[b]	20.6[b]	29.7	34.7[b]	44.2	14.2	57.4	40.3	45.8	80.7			Aromatics: 117.6[b],19.2[b],126.6[b],128.8 (2)[b] 123.7[e] 129.2[b] 138.5[b]						N-CH_2 56.6	CH_2Ph 32.6[b]	
3.59	20.1[b]	20.9[b]	29.9	36.7	46.9	14.3	58.4	42.7	43.4	80.6	43.1		158.4	106.3[b]	128.0[b]	118.1[b]	128.8[b]	141.3			
3.60[d]	21.8	25.1	30.8	40.4	49.0	16.0	56.1	50.4	36.7	28.8	44.3		158.0	115.1[b]	127.3[b]	120.2[b]	128.8[b]	139.2			
3.61	20.5	23.9	29.3	38.6	47.8	14.4	55.4	48.9	35.3	26.2	42.4		159.1	109.2[b]	126.0[b]	120.4[b]	129.6[b]	139.2			
3.62	23.7	25.5	32.8	35.3	47.2	96.2	59.2	51.2	41.3	67.8	42.3	56.1	144.5b	144.8[b]	118.4[b]	108.7[b]	124.4[b]	131.3[b]			

a : Free base in $CDCl_3$ with TMS as reference unless stated otherwise

b : Uncertain assignment. c : CD_3CN solvent. d : DMSO-d^6 solvent

e : $NCH_2\underline{C}H_2$ signal



Analytical Data Table 3.5

Compound	Formula		C	H	N
3.46	$C_{18}H_{22}N_2O_3$	Calc	68.77	7.05	8.91
		Found	68.69	7.08	9.06
3.51	$C_{20}H_{27}NO_4.H_2C_2O_4$	Calc	60.68	6.71	3.22
		Found	60.54	6.83	3.21
3.52	$C_{18}H_{25}NO_3.HCl.\frac{1}{2}H_2O$	Calc	61.97	7.80	4.01
		Found	61.96	7.48	3.77
3.53	$C_{18}H_{25}NO_2.HCl$	Calc	66.76	8.09	4.32
		Found	66.32	8.15	4.03
3.54	$C_{17}H_{23}NO_2.HCl$	Calc	65.90	7.81	4.57
		Found	65.50	7.91	4.40
3.55	$C_{19}H_{25}NO_3.HCl.\frac{3}{2}H_2O$	Calc	60.23	7.71	3.70
		Found	59.67	7.53	3.82
3.57	$C_{19}H_{25}NO_2.HCl.\frac{1}{2}H_2O$	Calc	66.17	7.89	4.06
		Found	65.83	7.45	4.19
3.58	$C_{24}H_{29}NO_2.HCl$	Calc	72.07	7.56	3.50
		Found	72.18	7.72	3.24
3.59	$C_{17}H_{23}NO.H_2C_2O_4$	Calc	65.69	7.25	4.03
		Found	65.13	7.64	3.60

3.60	$C_{17}H_{25}NO$	Calc	78.72	9.71	5.40
		Found	78.47	9.63	5.34
3.62	$C_{18}H_{25}NO_4$	Calc	67.69	7.89	4.38
		Found	67.30	7.99	4.36

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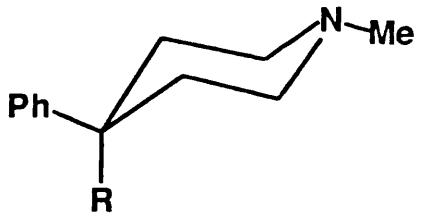
PIPERIDINE INTRODUCTION

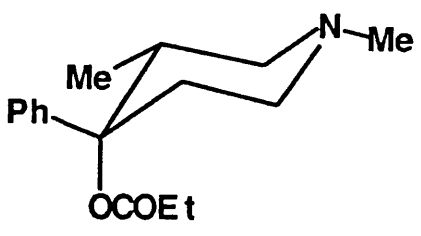
Pethidine 4.1 was originally synthesised in the 1930s during a search for spasmolytic drugs to replace atropine. It soon became apparent that pethidine possessed useful narcotic analgesic properties, and it has since become one of the most widely used synthetic narcotic analgesics. Due to its relatively short duration of action and moderate potency (approximately 1/7 that of morphine) it is widely employed in the control of labour pain.[1]



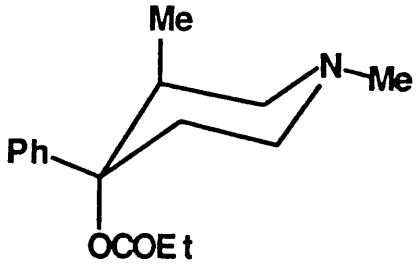
4.1 R=CO_2Et

4.2 R=OCOEt

The reversed ester of pethidine 4.2 is approximately 10 times more potent than pethidine itself both in rodent tests and in man.[2] The introduction of a 3-methyl substituent gives rise to the α-trans (3-Me/4-Ph) and β-cis prodines 4.3 and 4.4 respectively.



4.3



4.4

Racemic α-prodine 4.3 was previously marketed as Nisentil (now withdrawn) and is approximately equipotent with the des-methyl parent 4.2, whilst racemic β-prodine 4.4 is several times more potent. Resolution of β-prodine into its 2 antipodal forms showed the (+) antipode to be approximately twice as potent as the (-).[3]

Further studies revealed that the case of methyl was unique in that the α-trans derivative was the more potent when larger alkyl groups were substituted at the 3-position (table 4.1).[4]

	α (trans)	β (cis)
R	3-R/4-Ph	3-R/4-Ph
H	0.85	0.85
Me	0.92	0.18
Et	0.40	3.5
n-Pr	2.0	14.7
n-Bu	54.7	12.8
allyl	0.09	11.7

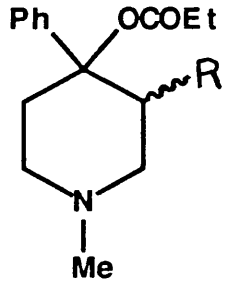


TABLE 4.1 [8] (ED_{50} mg/kg MHP)

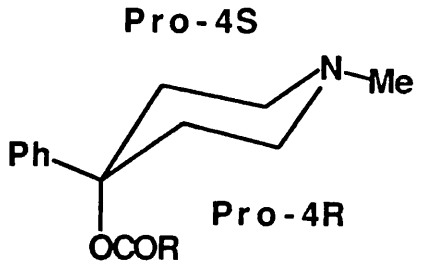
EFFECT OF INCREASING ALKYL CHAIN LENGTH ON ANALGESIC ACTIVITY OF SOME 3-ALKYLPIPERIDINE DERIVATIVES

(The α-3-allyl derivative is particularly potent: this is generally thought to be a consequence of enhanced binding of the allyl group to the receptor).

Over the past 20 years a large number of both mono and di (mostly) methyl substituted analogues of pethidine reversed esters have been reported. Most have been unambiguously configurationally and conformationally characterised using X-ray crystallographic and other methods, making it possible to discover whether the wide ranging potency variations could be rationalised in terms of the stereochemical requirements of the analgesic receptor.[5]

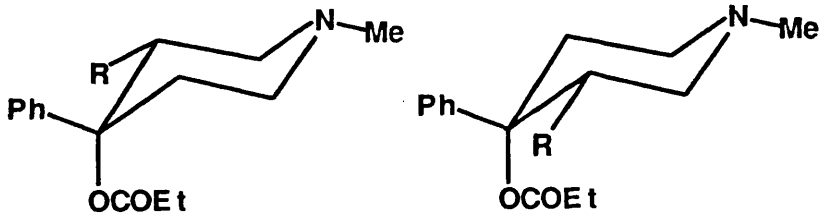
The results of this analysis will be summarised in this introduction. They have already been justified elsewhere largely in terms of a fit of the equatorial 4-phenyl chair conformation of the molecule at the receptor site rather than as a consequence of variation in metabolism or transport _in vivo_.[6]

Using biochemical nomenclature [7], the two sides of the ester 4.5 may be described as prochiral 4S and prochiral 4R.



4.5

If an alkyl group is introduced into the Pro-4S side the C-4 carbon atom becomes asymmetric and acquires an S configuration (Cahn-Ingold-Prelog convention [8]). Similarly, introduction of an alkyl group into the Pro-4R side gives C-4 an R configuration (figure 4.1). The potency data available on 3-alkylprodine derivatives tends to show that the opioid receptor discriminates between the Pro-R and Pro-S sides of the molecule. Thus, it is found that the more potent antipodes of α-3-alkyl 4.5 all have the same configuation when R = methyl, ethyl or propyl. Structure 4.6 shows the more (3R, 4S) and 4.7 the less (3S, 4R) potent antipode (table 4.2[9]).



R	4.6(3R,4S)	4.7(3S,4R)
Me	0.91	22.4
Et	0.90	25.0
n-Pr	1.0	25.2

TABLE 4.2 [9] (ED_{50} mg/kg MHP)

ANALGESIC ACTIVITIES OF SOME 3-α-ALKYL SUBSTITUTED PIPERIDINES

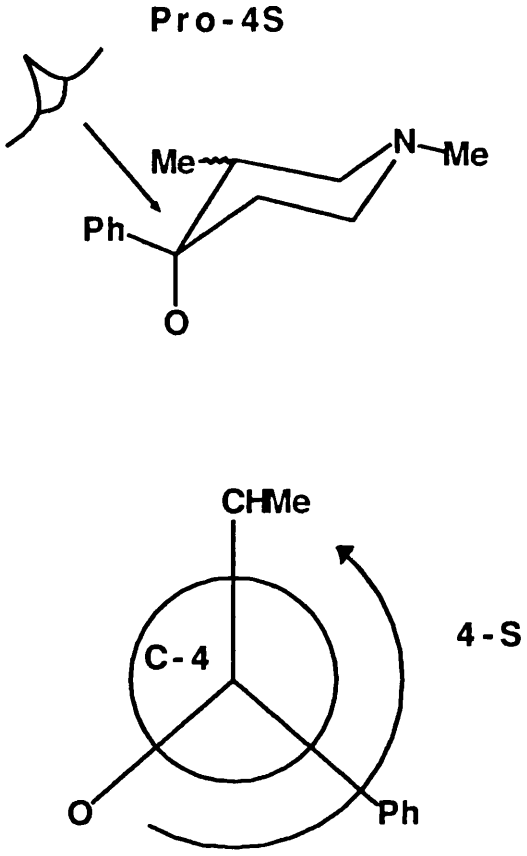
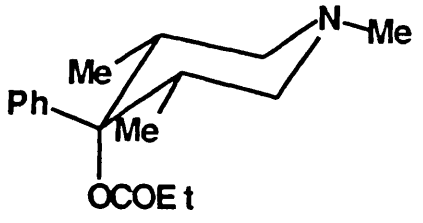


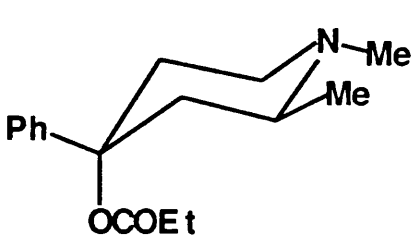
FIGURE 4.1 [2]

The results shown in the table 4.2 are consistent with the explanation that the molecule presents the Pro-4R side to the receptor. All the 4.6 derivatives therefore have very similar (high) potencies as their 3-R substituents do not hinder the approach to the receptor as do those of the 4.7 derivatives. This gives an essentially passive role to an 3-α-alkyl group in the Pro-4S side of the molecule. Consistent with this theory is the fact that 4.8 is inactive.[10]

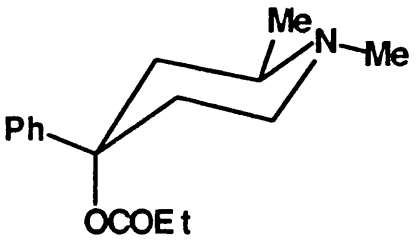


4.8

Investigations of derivatives with methyl substituents in the 2 position have found a significant potency reduction when an equatorial methyl is placed in the Pro-4S side of the molecule as in 4.10 (ED_{50} 5.5mg/kg), whereas 2-eq-methyl placed in the Pro-4R side has an essentially passive role 4.9, ED_{50} 0.53, c.f. 4.2, ED_{50} 0.50.

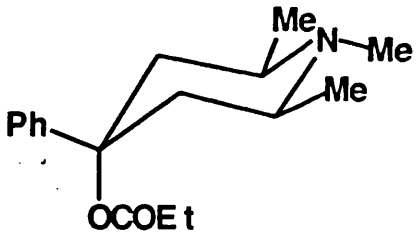


4.9



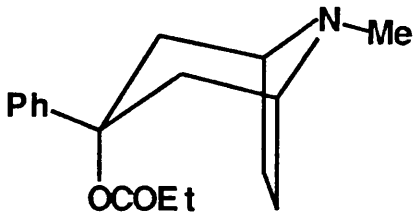
4.10

The cis-2,6-disubstituted derivative 4.11 is also consistent with this analysis, being inactive.[11]



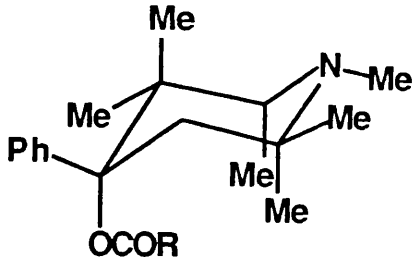
4.11

When a 2-methyl substituent is placed axially as in various disubstituted derivatives, activity is retained as exemplified by the tropane analogue 4.12 [12] which is slightly more potent than the corresponding unsubstituted prodine (4.2 with R=OCOMe). This insensitivity of the receptor towards axial 2-methyl is in marked contrast to its discrimination between equatorially placed 2-methyl substituents, as previously outlined.



4.12

The overall sensitivity of the receptor towards methyl substituents in pethidine reversed esters may therefore be summarised as in 4.13 where only favoured and passive (allowed) methyls are shown.

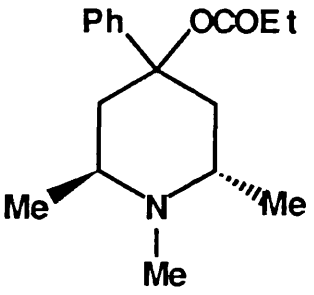


4.13

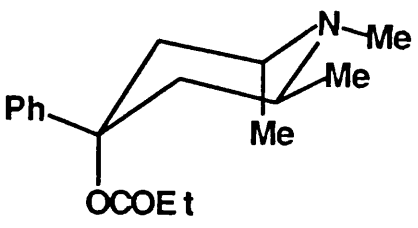
PIPERDINE DISCUSSION

In a recent study of the effect of methyl substitution in the piperidine ringe of pethidine reversed ester derivatives, a consistent set of structure-activity relationships was developed on the basis of the interaction of methyl groups with the opioid receptor. The absolute orientations of methyl groups which favour or have little influence with the receptor have been summarised in structure 4.13 (see introduction).

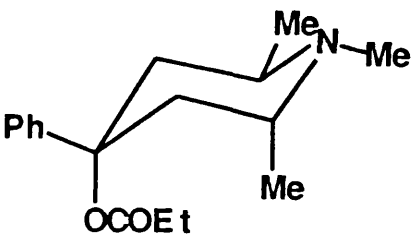
On the basis of this analysis it should follow that the antipodes of (±)-1-trans-2,6-trimethyl-4-phenyl-4-propionoxypiperidine hydrochloride 4.14 (the antipodal forms of which are illustrated by 4.15 and 4.16), should show a large potency difference with the more active form having the absolute configuration as depicted by 4.15 (2S, 6S).



4.14



4.15(2S,6S)



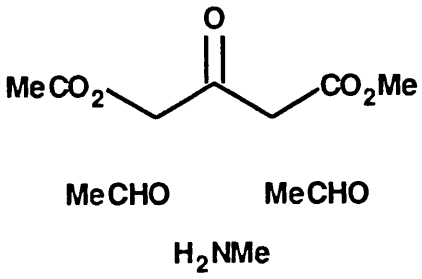
4.16(2R,6R)

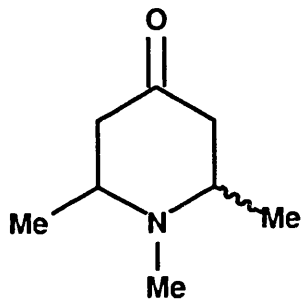
This discussion describes the synthesis and resolution of 4.14 into its 2 antipodal forms.[13]

Chemistry

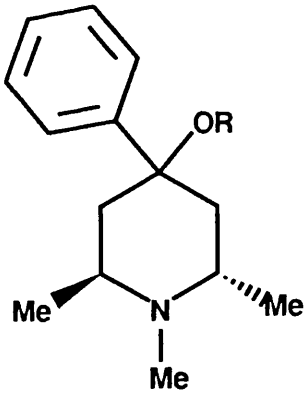
The required 1,2,6-trimethylpiperidone 4.17 was obtained by a Mannich reaction using dimethyl acetonedicarboxylate, acetaldehyde and methylamine hydrochloride (scheme 4.1 [11]). Reaction of 4.17 with phenyllithium in anhydrous ether followed by treatment with acetic anhydride gave the corresponding 4-acetoxy-1,2,6-trimethyl-4-phenylpiperidine 4.18. The ^{1}H NMR spectrum indicated that 4.18 had the trans configuration. Doublets at δ = 1.03 and 1.09 ppm were assigned to the axial and equatorial methyl groups respectively (figure 4.2). This was supported by the 22.5 MHz ^{13}C NMR spectrum of 4.18 which showed that four magnetically inequivalent methyl groups were present in the molecule (figure 4.3).

Resolution of 4.18 using (-)-tartaric, (-)-dibenzoyltartaric, (-)-ditoluoyltartaric, (+)-camphorsulfonic and (+)-bromocamphorsulfonic acid was attempted without success. Reduction of the acetyl group in 4.18 with lithium aluminium hydride (LAH) in anhydrous ether gave the corresponding piperidinol 4.19. This was successfully resolved using a molar quantity of (-)-dibenzoyl-L-tartatic acid with methanol as solvent. The optical activity of the salt remained constant after three crystallisations. The (-) base was then recovered from the crystallised salt. The base recovered from the mother liquors was mixed with a molar quantity of (+)-dibenzoyl-D-tartaric acid and the resulting salt was crystallised three times from methanol to give a salt with constant (+ ve) rotation.





4.17



4.18 R= COMe

4.19 R=H

SCHEME 4.1[11]

FIGURE 4.2

^{1} H 60 MHz NMR SPECTRUM OF 4.18 ($CDCl_3$ solvent, TMS ref.)

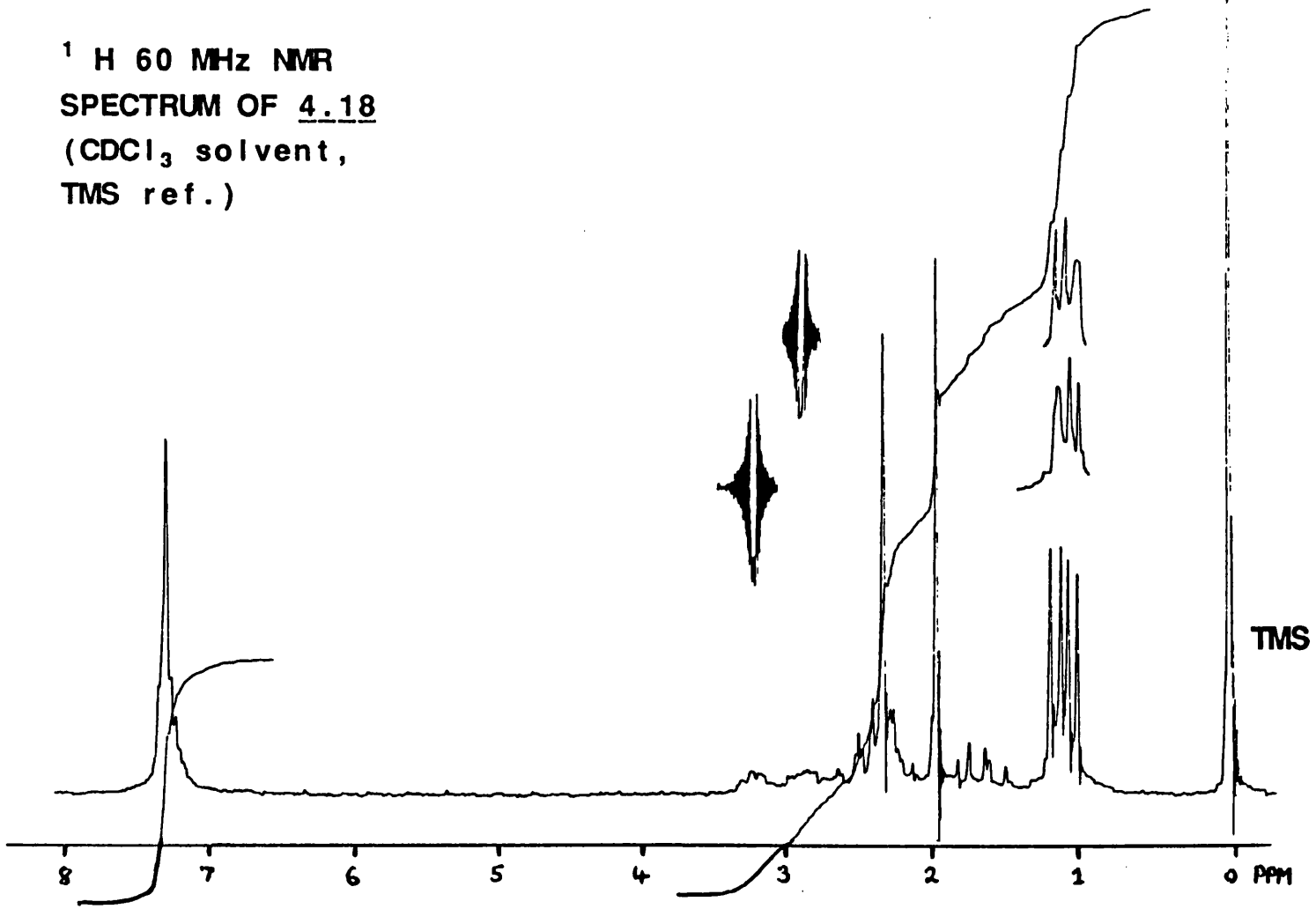
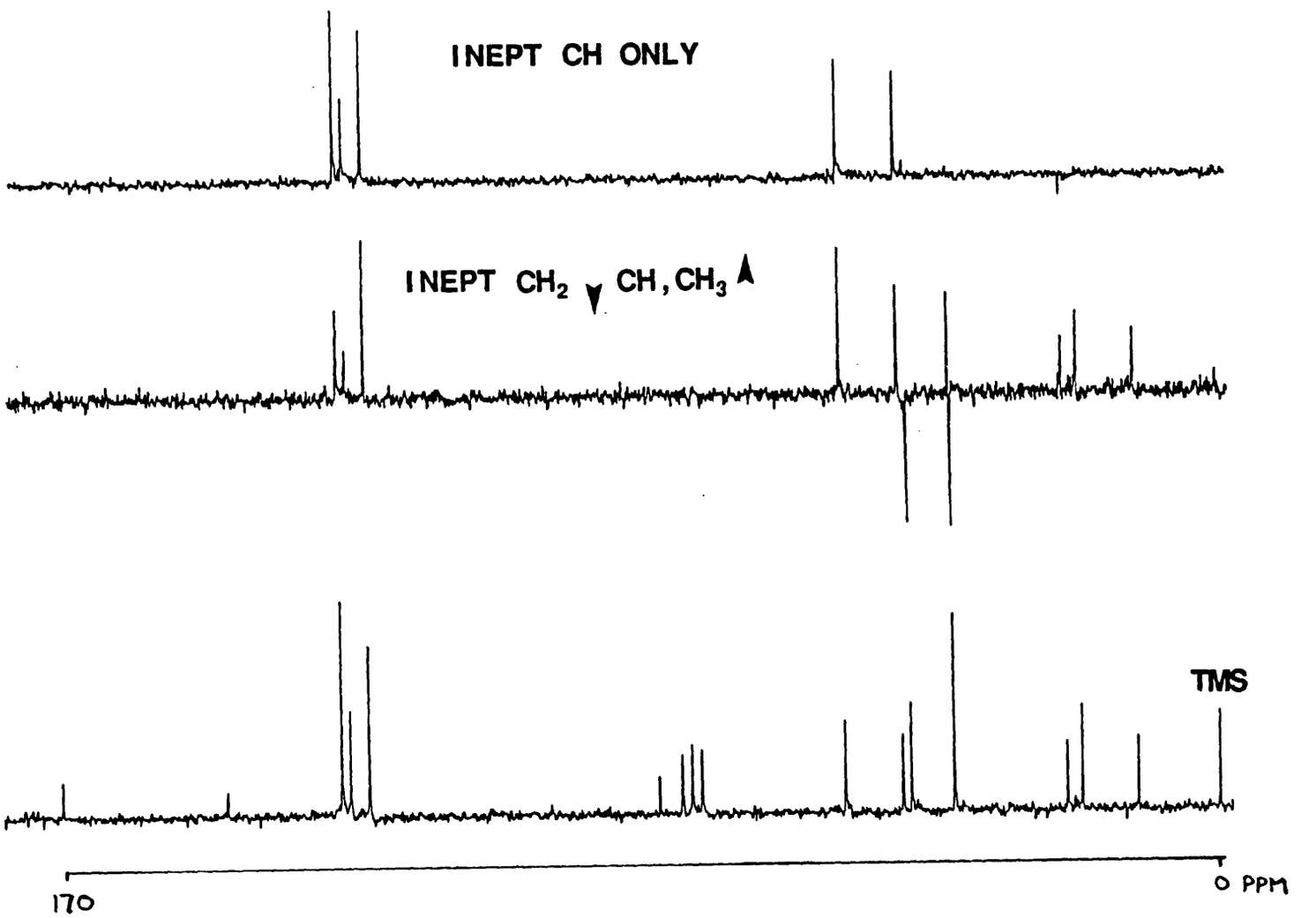
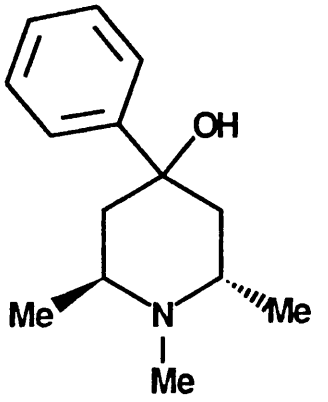


FIGURE 4.3

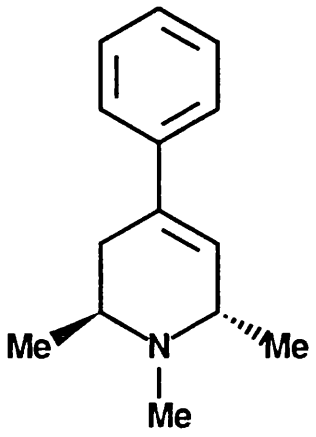
^{13} C 22.5 MHz NMR SPECTRUM OF 4.18 ($CDCl_3$ solvent, TMS ref.)



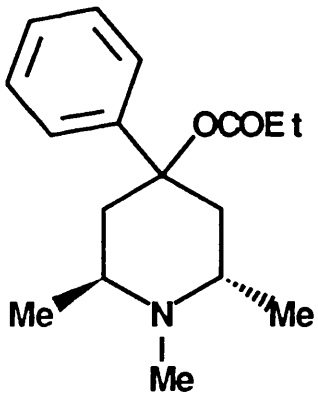
The (+) base was liberated from this salt and found to have a similar (but opposite) optical rotation to the (-) base (see experimental). Attempts to esterify the resolved piperidinols using acetic anhydride or acetyl choride gave mainly the dehydrated product 4.20, but reaction with acetic or propionic anhydride at 20°C in the presence of dimethylaminopyridine (DMAP) [14] was successful. Thus, reaction of (-) or (+) 4.19 with an excess of DMAP in propionic anhydride gave the corresponding (-) or (+)-1,2,6-trimethyl-4-phenyl-4-propionoxypiperidines 4.21 (scheme 4.2).[13]



4.19



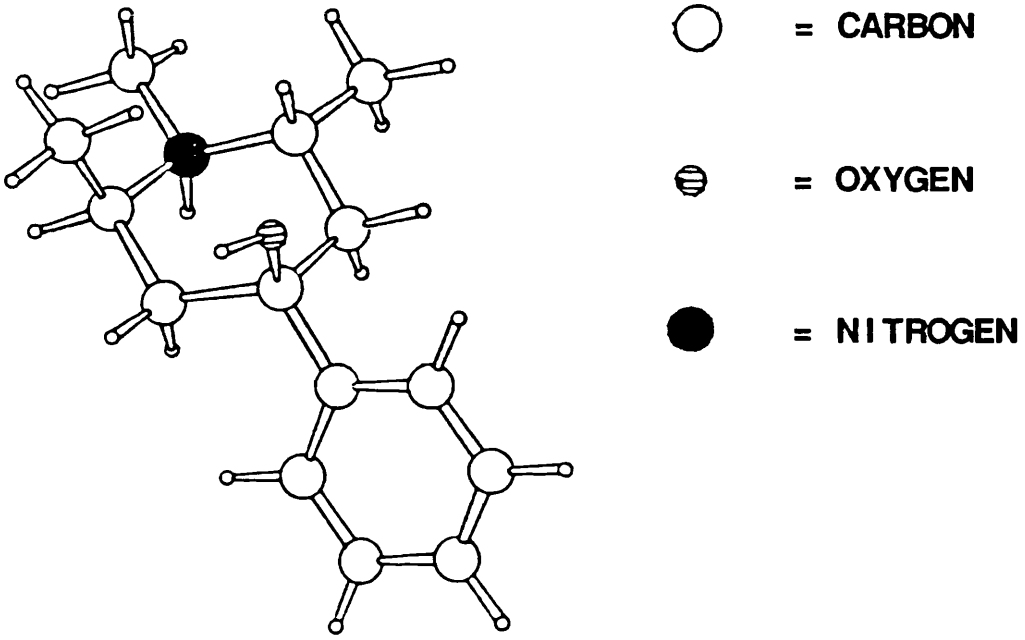
4.20



4.21

SCHEME 4.2 [13]

In order to find the absolute configuration of the (-) and (+) esters 4.21, X-ray crystallography was employed using the hydrobromide salt of (-) 4.19. The full details of the analysis (which are published elsewhere [15]) indicated that the absolute configuration of (-) 4.19 was 2R, 6R (figure 4.4).



CONFORMATION & ABSOLUTE CONFIGURATION OF (-) 4.19

FIGURE 4.4

Since the (-) piperidinol 4.19 yielded the (-) ester 4.21 and (+) 4.19 gave (+) 4.21, the absolute configurations are 2S, 6S for (+) 4.21 and 2R, 6R for (-) 4.21 as in diagrams 4.15 and 4.16 respectively.

Biological Activity

The results of testing racemic 4.21 and (-) and (+) 4.21 are shown in table 4.3. The (+) antipode of 4.21 was approximately 4 times more active than pethidine in the MHP whilst the (-) antipode of 4.21 was inactive at 20 mg/kg. A similar pattern of activity was seen in the tail flick and phenylquinone writhing tests with the (+) antipode (configuration 2S, 6S) showing significantly higher potency than the (-) antipode.

Conclusion

The more potent antipode of (±)-1-*trans*-2,6-trimethyl-4-phenyl-4-propionoxypiperidine was shown to have the absolute configuration 2S, 6S, which is consistent with the original hypothesis on the allowed pattern of methyl substitution in pethidine reversed esters.

TABLE 4.3

ANALGESIC ACTIVITIES OF (±) , (+) & (-) 4.21

Compound[a]	MHP[b]	MTF[c]	PPQ[d]
(±)4.21	1.5(1.1-2.1)	2.7(1.0-7.5)	0.1(0.03-0.5)
(+)4.21	1.1(0.9-1.3)	0.7(0.2-2.0)	0.2(0.07-0.7)
(-)4.21	IA[e] (5&20)	11.0(6.8-17.8)	3.0(1.9-4.7)

KEY FOR TABLE 4.3

a : Compounds tested as hydrochloride salts in water

b : Mouse hot plate test (ED_{50} mg/kg)

c : Mouse tail flick test (ED_{50} mg/kg)

d : Phenylquinone writhing test (ED_{50} mg/kg)

e : IA=Inactive at the dose levels indicated

Experimental Section

Infra-red spectra were recorded on a Unicam SP1025 spectrometer.

Melting points (uncorrected) were taken on a Gallenkamp melting point apparatus.

^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer operating at 22.5 MHz. The multiplicity of the resonances was obtained by either off-resonance (partial ^{1}H coupling) spectra, or by INEPT (Insensitive Nuclei Enhanced by Polarisation Transfer) spectra in which the phase of the signal indicated the number of protons attached to each carbon atom.

^{1}H NMR spectra were recorded using JEOL JNM-PMX 60 SI, JEOL PS100 and JEOL GX400 spectrometers. NMR samples (as bases unless stated otherwise) were prepared in 5mm o.d. tubes as approximately 10% solutions in $CDCl_3$ (unless stated otherwise) with TMS as reference.

Mass spectra were recorded on a VG 7070E mass spectrometer operating at 70 eV (EI).

Optical Rotations were measured on an Optical Activity Ltd AA-10 polarimeter.

Elemental analyses were performed by Butterworths Laboratories Ltd., Middlesex.

Formulae and abbreviations as used in the experimental section

$CDCl_3$	Deuterochloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
D_2O	Deuterium Oxide
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
HCl	Hydrochloric Acid
H_2SO_4	Sulphuric Acid
K_2CO_3	Potassium Carbonate
MeOH	Methanol
Me_2CO	Acetone
$MgSO_4$	Magnesium Sulphate (anhydrous)
NaOH	Sodium Hydroxide
Na_2SO_4	Sodium Sulphate (anhydrous)
$NaHCO_3$	Sodium Bicarbonate
Pr^iOH	Isopropanol
THF	Tetrahydrofuran
TMS	Tetramethylsilane

'Solvent was removed' - denotes evaporation under reduced pressure using a rotary evaporator.

1,2,6-Trimethyl-4-piperidone (4.17)[11]

To a stirred, cooled mixture of dimethylacetone dicarboxylate (100 ml), and acetaldehyde (64 ml) was added slowly a solution of methylamine hydrochloride (37 g) in H_2O (160 ml). After stirring at ambient temperature for 48 hours, excess acetaldehyde and H_2O were removed. To the residual yellow oil obtained was added a solution of concentrated hydrochloric acid (250 ml) in H_2O (150 ml) and the resultant solution held at 50°C for 16 hours to complete the decarboxylation. The cooled solution was basified with NaOH and extracted with CH_2Cl_2 (3 x 300 ml). Drying (MgSO4) and removal of solvent gave a brown oil which was distilled twice to give 4.17 (23.0 g, 19%) as a colourless oil b.p. 52-76°C @ 1 mmHg, (lit[11] b.p. 80°C @ 20 mmHg).

^{1}H NMR 1.03 δ (d, J = 6.5Hz, 3H, trans)

1.18 δ (d, J = 6.5Hz, 3H, cis)

2.28 δ (t, 3H, NCH_3, cis)

2.38 δ (t, 3H, NCH_3, trans)

4-Acetoxy-1,-(trans)-2,6-trimethyl-4-phenylpiperidine (4.18)[11]

To phenyllithium in anhydrous Et_2O [made from bromobenzene (111.3g, 0.71 mol) and lithium (10g, 1.42 mol), and left to react for 1 hour], was slowly added a solution of 4.17 (26g, 0.185 mol) in anhydrous Et_2O, and the mixture left to stir at ambient temperature for 24 hours.

The mixture was cooled and acetic anhydride (100 ml) was added slowly over 30 minutes, left to stir for 1 hour, then poured onto a mixture of ice (200g) and acetic acid (200 ml). The aqueous phase was separated and washed with Et_2O (2 x 500 ml). The combined ethereal extracts were washed with 50% acetic acid (3 x 200ml). The combined aqueous layers were basified with Na_2CO_3 and extracted with Et_2O (4 x 500 ml). Removal of solvent and drying ($MgSO_4$) gave crude 4.18 as a yellow oil. This was dissolved in Me_2CO and made acidic by addition of ethereal HCl. The hydrochloride salt of 4.18 was filtered and washed with Me_2CO.

Liberation of the free base gave 4.18 (26.1g, 54%) as a yellow oil. The hydrochloride crystallised from EtOH-Et_2O and had m.p. 198-200°C, (lit[11] m.p. 198-199°C).

^{1}H NMR
1.03 δ (d, J = 7 Hz, 2H, axCH_3)
1.09 δ (d, J = 7 Hz, 2H, eqCH_3)
1.72 δ (m, 2H, CH_2)
1.98 δ (s, 3H, $OCOCH_3$)
2.35 δ (s, 3H, NCH_3)
2.2 - 2.6 δ (m, 2H, CH_2)
2.9 δ (m, 1H, C (Hax)CH_3)
3.28 δ (m, 1H, C (Heq)CH_3)
7.3 δ (m, 5H, ArH)

^{13}C NMR See table 4.4

4-Hydroxy-1-(trans)-2,6-trimethyl-4-phenylpiperidine (4.19)[11]

To a stirred mixture of LAH (3.0g) in anhydrous Et_2O (100 ml) was slowly added a solution of 4.18 (20g, 0.09 mol) in anhydrous Et_2O (100 ml) and the mixture stirred for 30 minutes at ambient temperature. A saturated aqueous solution of Na_2CO_3 (20 ml) was added slowly dropwise with cooling and the mixture diluted with $CHCl_3$ (500 ml). Drying ($MgSO_4$), filtration, washing of the cake with $CHCl_3$ and removal of solvent gave 4.19 (16.3g, 68%) as a pale yellow solid, m.p. 90-3°C, (lit[11] m.p. 95°C).

The hydrobromide salt crystallised from EtOAc-EtOH as small prisms and had m.p. 156-7°C. These were subsequently used in the X-ray crystallographic analysis.

^{1}H NMR
1.03 δ (d, J = 7 Hz, axCH_3)
1.09 δ (d, J = 7 Hz, eqCH_3)
1.7 δ (m, 2H, CH_2)
1.75 δ (br s, 0H)
2.2 - 2.5 δ (m, 2H, CH_2)
2.32 δ (s, 3H, NCH_2)
2.6 δ (m, 1H, C (Hax)CH_3)
3.05 δ (m, 1H, C (Heq)CH_3)
7.3 δ (m, 5H, ArH)

^{13}C NMR See table 4.4

(-)-4-Hydroxy-1-(trans)-2,6-trimethyl-4-phenylpiperidine (-)4.19

A mixture of racemic 4.19 (16.7g, 0.076 mol) and (-)-dibenzoyl-L-tartaric acid monohydrate (28.7g, 0.076 mol) were dissolved in warm MeOH (130 ml), filtered and left to crystallise overnight. After 3 crystallisations of the salt from MeOH, 6.8g were obtained having a constant optical rotation, $[\alpha]_D^{20}$ - 76.0° (589 nm), - 351° (365 nm) (c 1, MeOH).

Liberation of the free base gave (-) 4.19 (2.5g, 30%) as a white solid. $[\alpha]_D^{20}$ - 17.0° (589 nm), -44.0 (365 nm), (c 1, MeOH).

(+)-4-Hydroxy-1-(trans)-2,6-trimethyl-4-phenylpiperidine (+)4.19

To 12.7g of the free base obtained from the mother liquor remaining after filtering off the first crop of (-) 4.19(-)-dibenzoyl-L-tartrate salt was added (+)-dibenzoyl-D-tartaric acid (21.8 g, 1 equivalent) and the mixture dissolved in warm MeOH and left to crystallise as before. After 3 crystallisations from MeOH, 8.0g were obtained having a constant optical rotation, $[\alpha]_D^{20}$ + 71.0° (589 nm), + 352° (365 nm). (c 1, MeOH). Liberation of the free base gave (+) 4.19 (2.7g, 32%) as a white solid. $[\alpha]_D^{20}$ + 17.0° (589 nm), + 44.0° (365 nm), (c 1, MeOH).

1,(trans)-2,6-Trimethyl-4-phenyl-4-propionoxypiperidine (4.21)

To a stirred solution of 4.19 (0.5g, 0.0023 mol) in propionic anhydride (5 ml) was added dimethylaminopyridine (DMAP) (0.15g), the resulting solution kept at ambient temperature for 24 hours, then poured onto a 50% aqueous solution of acetic acid (50 ml). The solution was washed with Et_2O (3 x 75 ml: discarded), basified with Na_2CO_3 and extracted with Et_2O (3 x 100 ml). The combined ethereal extracts were washed with H_2O (10 x 50 ml) to remove DMAP then dried ($MgSO_4$) and solvent removed to give 4.21 (0.46g, 73%) as a pale yellow oil, b.p. 100°C @ 2mm Hg (dec). The hydrochloride crystallised from EtOAc/EtOH and had mp 186-7°C.

IR (KCl,Hydrochloride) 1745 cm^{-1} (C=O)

^1H NMR
1.05 - 1.25 δ (m, 9H, 3 x CH_3)
1.4 - 2.50 δ (m, 6H, 3 x CH_2)
3.25 δ (s, 3H, NCH_3)
2.75 δ (m, 1H, C(Hax)CH_3)
3.05 δ (m, 1H, C(Heq)CH_3)
7.05 δ (m, 5H, ArH)

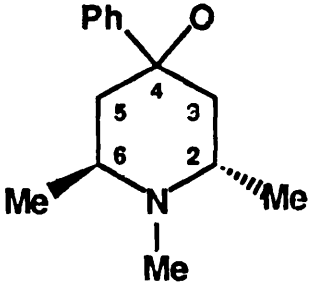
^{13}C NMR See table 4.4

Analysis See table 4.5

TABLE 4.4 ^{13}C NMR DATA OF SOME 1,2,6-TRIMETHYL-4-PHENYLPIPERIDINES

Compound[a]	N-Me	C_2	C_3	C_4	C_5	C_6	2 - Me axial	6 - Me equat-orial	Aromatics	C = O	$COCH_2$	CH_2CH_3
4.18	39.0	46.4	45.2	81.9	39.0	54.8	12.0	20.3	145.1, 128.3, 127.0, 124.3	169.5	-	22.5
4.19	39.1	47.1	46.6	73.2	43.4	54.8	13.3	19.8	149.1, 128.1, 126.7, 124.5	-	-	-
4.21	38.9	46.4	45.1	81.6	39.1	54.8	12.1	20.3	145.3, 128.3, 127.0, 124.2	172.8	28.9	8.9

a : Free base in $CDCl_3$ with TMS as reference



Analytical Data Table 4.5

Compound	Formula		C	H	N
4.21	$C_{17}H_{25}NO_2 . HCl$	Calc	65.48	8.40	4.49
(±) 4.21		Found	65.30	8.37	4.29
(+) 4.21		Found	65.20	8.42	4.28
(-) 4.21		Found	65.46	8.37	4.26

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